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- Educational Symposia
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TH-OR01
The Relationship Between Intravenous Fluid Administration and Renal Outcomes After Angiography
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Background: Contrast associated AKI (CA-AKI) may result in prolonged hospital stay and increased mortality. Fluids remain the mainstay for prevention. There is a lack of consensus on the optimal fluid rate and amount. Using the PRESERVE dataset, we studied the effect of peri-procedure fluid administration strategies on CA-AKI and 90-day need for dialysis, death, or a ≥50% increase in serum creatinine.

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

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

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

TH-OR02
AKI in Patients Treated with Immune Checkpoint Inhibitors
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Background: Data on immune checkpoint inhibitor-associated acute kidney injury (ICPi-AKI) are largely limited to single-center case series. We performed a multicenter study, the largest to date, to investigate risk factors, clinico-pathologic features, outcomes, and survival in patients with ICPi-AKI.

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

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

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

TH-OR03
The Incidence and Risk Factors of AKI Among People with HIV on Antiretroviral Treatment
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Background: The epidemiology of hospitalized acute kidney injury (AKI) among people with HIV (PWH) in the era of modern antiretroviral therapy for all PWH is not well-characterized.

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

Results: Most participants (75%) were Black, 34% were female, mean age was 43 years and mean eGFR 106 mL/min/1.73 m². The incidence of AKI fluctuated annually, peaking at 40 per 1,000 person-years (PY) (95% CI: 22-69) in 2007, and reached a nadir of 20 per 1,000 PY (95% CI: 11-34) in 2010 (Figure). After multivariable adjustment, characteristics independently associated with AKI included Black race (HR=2.44; 95% CI: 1.42-4.20), hypertension (HR=1.61; 95% CI: 1.09-2.38), dipstick proteinuria ≥1+ (HR=1.78; 95% CI: 1.06-2.97), history of AIDS (HR=1.82; 95% CI: 1.29-2.56), CD4 count <200 cells/mm³ (HR=1.46; 95% CI: 1.02-2.07), and lower serum albumin (HR=2.87 per 0.1 mg/dL; 95% CI: 2.78-2.97).

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

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

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

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

Results: There were 4,596/3,035 (13.6%) patients with at least one day of high-NTMx exposure, and 17,254/144,997 (11.9%) of hospital days met high NTMx exposure criteria. AKI of any etiology was seen in 3,398 (10%) of patients, of which 1,467 (43.2%) were from high-NTMx exposure, and 1,131 NTMx-AKI events, for an AKI rate of 18.7% following high NTMx exposure. NTMx-AKI preceded AKI development, by a median of 5 days. There were 6,038 total exposures and 1,131 NTMx-AKI events, for an AKI rate of 18.7% following high NTMx exposures. Serum creatinine was checked on 89% of days on or within 48 hours of high NTMx exposures.

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

Proton Pump Inhibitor Exposure and Risk of AKI after Cardiac Surgery

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

Methods: This retrospective study was conducted by analyzing two cohorts based on tertiary hospital-based electronic medical records and nationwide health insurance information. The Severance cardiac surgery cohort consisted of 6,555 patients aged 18 years who underwent cardiac surgery between May 2011 and 2010. From the National Health Insurance Service-senior (NHIS-senior) cohort, 2,939 patients aged 60 years who underwent cardiac surgery between 2004 and 2015 were selected. Preoperative PPI exposure was defined as a PPI prescription record within 3 weeks before cardiac surgery. Primary outcome was AKI requiring dialysis (AKI-dialysis) and secondary outcomes were in-hospital mortality and hospital and intensive care unit (ICU) stay durations.

Results: In the Severance cardiac surgery cohort (mean age, 62.0 years; male, 60.1%) who was propensity score matching, accidental AKI-dialysis (5.3% vs. 3.2%, P = 0.002) and in-hospital mortality (4.7% vs. 3.2%, P = 0.038) were significantly higher among PPI-exposed than PPI-non-exposed patients. In addition, median (IQR) hospital stay durations were longer in patients exposed to PPI than in those who were not. Multivariable conditional logistic analyses revealed that PPI exposure was significantly associated with AKI at 90 (HR 3.04; 95% CI 2.98-3.09) and 365 days (HR 2.39; 95% CI 2.36-2.42) and in-hospital mortality (OR, 1.53; 95% CI 1.03-2.27). The NHIS-senior cohort (mean age, 72.4 years; male, 58.7%) revealed comparable findings, showing that PPI exposure was significantly associated with incident AKI-dialysis (OR, 2.29; 95% CI, 1.60-3.39) and in-hospital mortality (HR, 1.87; 95% CI, 1.48-2.37).

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

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

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

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

Results: We identified 28,871 patients with AKI, of whom 21,452 were matched 1:1 to similar patients without AKI. Acute kidney injury was associated with a 7% (95% CI 5.9-8.3%) lower likelihood of receiving all 3 cardiovascular drug classes within 1 year of hospital discharge. This result was largely driven by a 13% (95% CI 11-15%) lower likelihood of ACEI/ARB prescription across all categories of AKI severity. Lower use of beta-blockers and statins was observed in severe AKI. Conversely, AKI was associated with a more frequent use of losartan (shR=2.03; 95% CI 1.17-3.23) and mineralocorticoid receptor antagonists (shR=1.12, 95% CI 1.15-1.28). The use of most medications stabilized at 3 months post-AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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

TH-OR08 IMPROVE AKI: A Cluster-Randomized Trial of Team-Based Coaching Interventions to Improve AKI

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

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

Results: Across 20 randomized Veterans Administration medical centers, there were 4,517 patients including 1,153 patients with pre-existing chronic kidney disease (CKD) and 804 patients with AKI in the TA+ASR and VLC+ASR clusters, resulting in a strong yet non-significant effect among CKD patients (aOR: 0.76; 0.46, 1.24). In all patients, the VLC+ASR intervention cluster had a substantial 4.5% decrease in AKI incidence compared to TA alone (aOR: 0.76; 0.46, 1.24). The TA+ASR combination also showed a 1.4% reduction in AKI compared to TA alone (aOR: 0.96; 0.58, 1.57).

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

Funding: NIDDK Support

Figure 1: Team cluster randomized trial to prevent acute kidney disease with site-level random effects for all cardiac catheterization patients and those patients with chronic kidney disease.

TH-OR09 Properties of Proenkephalin (penKid) in Septic AKI

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

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

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

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

TH-OR10 Renal Outcomes After Chimeric Antigen Receptor T Cell (CAR-T) Therapy: A Single-Center Perspective

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

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

Results: With an average age of 58.7 years (SD±10.5), 24 males and 15 females, 14/39 had mild CKD (i.e <90 ml/min/1.73 m²) and 4/39 had moderate CKD (i.e ≤60 ml/min/1.73 m²). CKD was observed in 22/39 (56%) and ICU care in 6/39 (15%) cases. Of the 9 AKI cases (6 classes 1, class 2, class 3, class 5, resolved, 2 progressed and 2 patients expired. There were a total of 10 deaths (8-678 days after CAR-T). Unirradiantly, there was a correlation between underlying hypertension and AKI with death (RR (95% CI) = 3.4 (1.8, 6.1), p=0.004), (ICU, RR (95% CI) = 5.0 (1.8, 13.9), p=0.004), ICU correlation with AKI (RR (95% CI) = 4.4 (1.6, 11.8), p=0.02), but there was no association between CRS and the development of AKI. Multivariate survival analysis didn’t find any difference between patients with and without CKD.

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

TH-OR11 Treatment of Osteoporosis in CKD5D Patients Based on Bone Turnover: A Randomized Controlled Trial Showing Better Survival in Patients with Non-High Turnover

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Background: Bone turnover in osteoporotic CKD5D patients (pts.) may be elevated (HTO) or low (Non-HTO). HTO is associated with poor renal outcome. Patients with HTO may potentially benefit from therapy aimed at reducing bone turnover. There is no information on a tailored approach to treatment based on bone turnover. In HTO, characterized by excessive bone turnover, it makes sense to use antiresorbers, while they should be avoided in NHTO. Methods: 119 adult CKD-3D pts. with DXA t-scores < -1.0 were enrolled into this 12 month trial. Pts. were classified as HTO or NHTO based on race-specific cutoff values of serum PTH. NHTO pts. were randomized into treatment (Trrs) with teriparatide or standard of care (Ctrl). In HTO pts. treatment with Alendronate or Ctrl. Demographic and clinical data, lab values, DXA and QCT total hip BMD, and MSQCT measurements of bone structure were obtained at baseline and 12 months. Outcomes were changes in BMD and aortic calcification (AAC). Declaration of Helsinki was followed. There were 48 NHTO and 71 HTO pts. The median total PTH was 183 (IQR 138-337) in the NHTO group and 669 (IQR 502-1068) in the HTO group. Treatment groups and turnover arms were well balanced relative to patient race (34% AA), sex (57% m), age (61.0 ±12.5 y), diabetes vintage (4.7 ± 4.0 y), and DXA t-score (-2.9 ± 6.7). Throughout the study, 37 pts. withdrew due to transplantation and personal reasons.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Bone loss was improved in treated NHTO pts. (Trx: +5.7 g/cm² ±SE 4.7 vs. Ctrl:-10.7 ±SE 4.7, p=0.019) but not significantly in HTO pts. (Trx: -0.2 g/cm² ±SE 5.7 vs. Ctrl: -3.5 ±SE 3.4, p=0.377). ΔAC was higher in the HTO arm (NHTO: 4.5 ±SE 1.6 vs. HTO: 8.7 ±SE 1.4, p=0.049) and lower in African Americans (AA: 3.6 ±SE 1.7 vs. White: 8.8 ±SE 1.4, p=0.017). The multivar. ΔAC regression coefficient for HTO vs. NHTO was 5.0 (95% CI 0.9-9.2, p=0.019) and for AA vs. White was -5.4 (95% CI -9.6-1.1, p=0.013). In the NHTO group there were 0 deaths compared to 18% deaths in the HTO group (11 deaths, p = .005).

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

Funding: NIDDK Support, Private Foundation Support

TH-OR12
The Calcified Vasculature in CKD Secretes Signal Proteins That Inhibit Bone Mineralization
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Background: Our group has recently demonstrated that CKD-induced vascular calcification impairs bone formation & mineralization in an in vivo model by transplanting calcified aortas from CKR rats into healthy recipients. Aim was to confirm our hypothesis of a direct crosstalk between the vasculature & bone in in vitro experiments.

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

Results: CA completely inhibited mineralization in UMR-106 cells (Figure 1). Mineralization inhibitor osteopontin (OPN) mRNA & protein were highly upregulated in UMR/CA (OPN mRNA UMR/CA 23.50 [5.53-51.06], UMR/NA 2.78 [1.20-7.85], UMR 0.80 [0.39-5.49], p<0.001). Induction of OPN was abolished by LiCl. ANKH was upregulated in UMR/UA (2.95 [1.87-7.32], UMR/NA 1.75 [0.51-2.46], UMR 0.96 [0.49-2.15], p<0.001), whereas same levels of ApoL were found. Similar expressions of β-catenin protein & Wnt target genes c-Myc & Ccdn1 were found. However, Jun was upregulated in UMR/NA & UMR/CA (UMR 0.94 [0.61-2.83] vs. UMR/NA 1.58 [1.18-2.29] vs. UMR/CA 1.98 [1.08-3.44], p<0.001). The CA secreted large amounts of Scl (1936 [495-4400] vs. NA 31 [7-88] pg/ml, p=0.002), Dkk1 (353 [110-686] pg/ml vs. none in NA), and Act A (12158 [4712-18000] vs. NA 1838 [250-4146] pg/ml, p=0.002). NTS was secreted SFRP4.

Conclusions: This study confirms the hypothesis of a direct crosstalk between vasculature and bone. The uremic calcified aorta secretes signal molecules that inhibit bone mineralization.

Funding: Private Foundation Support

TH-OR13
HIF-PHI Have Direct Actions in Osteocytes: Implications for Anemia Treatment in CKD
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Background: Patients with CKD manifest overlapping oxygen sensing/endocrine dysfunction as osteocyte-produced FGF23 is highly elevated under prevailing anemia, however the cellular mechanisms driving FGF23 production are not understood. Our goal was to test the molecular context of osteocyte oxygen sensing, and the roles of these systems in FGF23 induction which can have severe effects on CKD bone disease.

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

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

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

Funding: NIDDK Support, Other NIH Support - NHLBI, NIAMS
TH-OR14

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

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

Methods: We performed a two-sample MR study to assess the causal association of FGF23 with overall heart failure and heart failure subtypes. Instrumental variables were defined as independent SNPs associated with FGF23 genotype-wide: rs17479506, rs11741640, rs9292537, rs17216707, and rs2769071. Summary-level data from the HERMEs consortium and individual-level data from BioVU, was used to examine associations of the 5 SNPs with incident heart failure and subtype. We additionally developed an eGFR polygenic risk score based on CKD-GED summary statistics, composed of SNPs associated with eGFR at p<5 x 10^-8, and dichotomized the eGFR PRS at one SD above the mean.

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

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

Funding: NIDDK Support

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

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TH-OR15

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

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

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

Results: From libraries of 10,000 male/female kidney cells, 21 UMAP clusters enriched markers distinctly identified epithelial, endothelial, and immune cells. At baseline, KL mRNA had diffuse expression in proximal tubule (PT) S1-S3 cells, overlap in loop of Henle, and was more concentrated in distal/connecting tubule (DT/CNT). In response to FGF23, at 1h Egr1, other MAPK genes, and eIF2 signaling were increased, tracking with 80% of KL-positive PT and DT cells. The vitamin D 24-OHase (Cyp27b1), other MAPK genes, and eIF2 signaling were increased, tracking with 80% of KL-positive PT and DT cells. The vitamin D 24-OHase (Cyp27b1), other MAPK genes, and eIF2 signaling were increased, tracking with 80% of KL-positive PT and DT cells.

Conclusions: At later time points, PXR signaling was specific to PT, and Epithelial Remodeling and Actin-based Motility signaling to DT. We demonstrated that FGF23 bioactivity controls nephron segment-unique and -general transcriptional responses in vitro essential to regulate mineral metabolism. Identification of these pathways is critical for the isolation of novel disease targets.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR16

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

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

Methods: To distinguish between the individual and combined effects of FGF23, phosphate and iron in CKD, we fed WT and Cola4a30x mice (CKD model) from 4-10wks either control (Ct), low iron (LI), low phosphate (LP), 1% carboxyl iron (CI) or ferric citrate (FC) diets. To further study the role of iron in CKD, we compared the effects of these diets in mice receiving iv ferric dordosmale (FD) using biochemical, histological and RNAseq analyses.

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

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

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

TH-OR17

Critical Role of Osteopontin in Maintaining Urinary Phosphate Solubility in CKD

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

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

Results: OPN protein expression is markedly increased in all tubular segments in mouse models of cystic kidney disease (pcy/pcy), glomerulonephritis (Cola4a3), and chronic tubulointerstitial injury (alcoholic acid). In Cola4a3 mice with slowly progressive CKD, kidney OPN expression and urinary OPN-Cr increased before gross histologic changes in the kidney or a rise in BUN, serum Cr, FGF23 and PTH. Unilateral nephrectomy studies in wild-type mice proved that nephron reduction alone was sufficient to increase tubular OPN production. Induction of CKD in OPN-null mice fed a high phosphate diet led to severe nephrocalcinosis (Figure 1). Lastly, pharmacologic neutralization of the ASARM motif of OPN in phosphaemic mice resulted in severe nephrocalcinosis that mimicked OPN-null CKD mice.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Figure 1. Induction of CKD in Spp1 (OPN-null) mice results in severe nephrocalcinosis. Whole kidney uCT images demonstrating severe nephrocalcinosis in Spp1 mice fed a high phosphate diet (1.1%) did not induce CKD induction by either ingestion of 0.2% adine or IP injections of ariloxic acid.
TH-OR18
Tenapanor Controls Serum Phosphorous and Reduces PTH and FGF-23 in Patients on Dialysis with Severe Secondary Hyperparathyroidism
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1Dialysis Clinic Inc, Boston, MA; 2Tufts University School of Medicine, Boston, MA; 3Ardelyx Inc, Fremont, CA.

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

Methods: The phase 3 PHREEDOM trial evaluated the safety and efficacy of tenapanor in patients on dialysis with hyperphosphatemia. Following washout from binders, patients whose serum phosphorus (sP) increased by ≥1.5 to 6.0 mg/dL were randomized. Those randomized to the tenapanor arm received tenapanor 30 mg PO BID for 26 weeks. Serum calcium (SCa), sP, PTH, and FGF23 were measured per protocol.

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

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

Funding: Commercial Support - Ardelyx, Inc.

TH-OR19
Initial Evaluation of High-Dose Extended-Release Calcifediol (ERC) in Patients with Stage 5 CKD on Hemodialysis (HD)
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Background: ERC has been approved since 2016 for treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3-4 CKD and vitamin D insufficiency at weekly doses of 210 or 420 mcg (30 or 60 mcg/day). Conversion of calcifediol to calcitriol is a key role of the CC in regulating the proliferation in the PTGs.

Methods: Adults with stage 5 CKD on regular HD with iPTH >600 pg/mL and at least one post-baseline PTH ≥6.0 mg/dL were treated patients with baseline PTH >600 pg/mL and at least one post-baseline PTH measure (n=73).

Results: The goals of the study were to: (1) evaluate whether these patients could tolerate weekly doses of 210 or 420 mcg (30 or 60 mcg/day). Conversion of calcifediol to calcitriol supporting a belief that normal serum levels of 1,25-dihydroxyvitamin D (1,25D) cannot exceed 60 pg/mL. Tenapanor in patients on dialysis with hyperphosphatemia. Following washout from binders, patients whose serum phosphorus (sP) increased by ≥1.5 to 6.0 mg/dL were randomized. Those randomized to the tenapanor arm received tenapanor 30 mg PO BID for 26 weeks. Serum calcium (SCa), sP, PTH, and FGF23 were measured per protocol.

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

Funding: Commercial Support - OPKO Health

TH-OR20
Parathyroid-Specific Knockout of Core Circadian Clock Gene Bmal1 Increases Proliferation of the Parathyroid Gland in CKD
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Background: Proper rhythms in metabolism, hormone secretion and cell cycle are maintained by a molecular circadian clock (CC) in the CNS as well as in peripheral tissues. The transcription factor Bmal1 is a major component of the CC. We have previously shown that an internal CC operates in the parathyroid gland (PTG) and that it is disturbed in uremia. We constructed a PTG-specific Bmal1 knockout mouse to investigate the function of the PTG clock in health and in CKD.

Methods: PTG-specific knockout of Bmal1 was generated by crossing PTHcre mice with Bmal1fl/fl mice (WT) giving rise to PTHcre; Bmal1+/−/+ mice (KO). Blood samples and PTGs were harvested at 4h interval. CKD was induced by feeding mice an adenine diet for 3 weeks. Gene expression was examined by qPCR, protein expression by western blot and proliferation by Ki-67 labeling. Circadian rhythmicity was assessed by cosinor analysis.

Results: Bmal1 protein was reduced by 77% in the PTGs of KO mice and circadian rhythmicity of Bmal1 gene expression was abolished along with abolishment of rhythmicity in clock genes Cry1 and Cry2 (p<0.0001) in 4h sampling of clock genes Per2 (p=0.001), Cry1 (p=0.0001) and Cry2 (p=0.0001), compared to WT. The disturbed clock in KO resulted in abrogated rhythmicity of clock-controlled cell cycle regulator Wee1 (KO p=0.16, WT p=0.0016) and of regulators of parathyroid proliferation Gcm2 (KO p=0.03, WT p=0.03) and Gata3 (KO p=0.84, WT p=0.01). Gata3 was upregulated compared to WT (p<0.01). Plasma PTH was significantly rhythmic in both KO and WT mice. In a basal condition the phenotype of KO mice was similar to WT, regarding weight, femur length, basal PTH levels and secretory response to hypocalcemia. Uremia significantly increased the PTG Ki-67 labeling index in KO compared with WT (7.0% vs. 2.4%, p=0.036).

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

TH-OR21
mTOR-Activating Mutations in RRAGD Cause Kidney Tubulopathy and Cardiomyopathy (KICA) Syndrome
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Background: Over the last decades, advances in genetic techniques have resulted in the identification of rare hereditary disorders of renal magnesium and salt handling. Nevertheless, ≥20% of all tubulopathies patients remain without genetic diagnosis. Here, we explore a large multicentric patient cohort with a novel inherited salt-losing tubulopathy, hypomagnesemia and dilated cardiomyopathy (DCM).

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

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

Conclusions: Our findings establish a novel disease phenotype combining kidney tubulopathy and cardiomyopathy (KICA) caused by an activation of mTOR signaling suggesting a critical role of Rag GTPase D for renal electrolyte handling and cardiac function.
**TH-OR23**

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

Jessica P. Bahena-López,1 María Chavez-Canales,2 Ju Hye Lee,3 Adrian R. Murillo-de-Orozos,1 Norma H. Vázquez,4 David H. Ellison,5 María Castañeda-Bueno,1 Gerardo Gamba,1,2

Background: The physiological role of KS-WNK1 in the distal convoluted tubule is not yet elucidated. KS-WNK1 upregulates NCC through activation of WNK4-SPAK signaling, and loss of function mutations in distal tubular system. We recently demonstrated that local K+ concentration could be sensed by PCs to activate ENaC through mTORC2-SGK1 signaling, and suggested a role for WNK1 in this mechanism. However, the mechanistic basis of this regulation has not been explored. In DCT, WNK4 modulates NCC activity in response to extracellular K+ in a kinase-dependent manner. Here we have explored the role of WNK1 and 4 in local sensing of extracellular potassium concentration.

Methods: Using WNK1 and 4 knock-out (KO) mice, wild type mice were exposed to dietary potassium restriction (0KD, 0.56 mEq/l, p<0.05, respectively) and WT mice K+ 0.20 vs KS-KO 2.44 ±0.31, a.u., p<0.01. KS-KO mice, as occurred in WT mice (WT 1.00 ±0.20 vs KS-KO 2.44 ±0.31, a.u., p<0.01), showed reduced NCC activity. The results at the end of 0 KD, serum K+ was significantly lower in KS-KO mice than in WT mice (p<0.05), while NKCC phosphorylation was higher in the WT mice (n=3, in MT-T). Variants segregated with the phenotype and were near homoplasmic in affected individuals. Importantly, affected members of six families with an MT-TF variant additionally suffered from progressive chronic kidney disease (CKD). Kidney biopsies in two affected individuals showed abnormal mitochondria, especially in the distal tubule. Maximal mitochondrial respiratory capacity was reduced in patient fibroblasts, caused by dysfunction of oxidative phosphorylation complex IV. In vitro pharmacological inhibition of complex IV, mimicking the effect of the mtDNA variants, demonstrated an inhibitory effect on NCC activity and NCC-mediated sodium uptake under low potassium diet. Therefore, we have explored the role of WNK1 and 4 in local sensing of extracellular potassium concentration.

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

Funding: Private Foundation Support. Development Support - Non-U.S.

**TH-OR24**

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

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

Results: In WT mPCCD cells, extracellular K+ stimulated ENaC activity and phosphorylation, Nedd4-2 phosphorylation and ENaC current concomitant with cleaved ENaC. In WT cells, inhibition of WNK kinase activity by WNK463 had no significant effect on ENaC phosphorylation, ENaC activity, and ENaC phosphorylation and ENaC activity. Furthermore, this effect was accompanied by greater association of SGK1 with both mTORC2 and WNK1 (WT or kinase-dead). KS-KO mice and the recovery of WNK4 expression, had similar effects to WNK1 on SGK1 phosphorylation and ENaC current.

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

Funding: NIDDK Support, Private Foundation Support.

**TH-OR25**

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

Steven G. Coça,1 Christopher G. Rowan,2 Paula J. Alvarez,3 Ladan Golestanesh,4 Nilmar Desai,5

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

Methods: This retrospective, propensity score–matched cohort study utilized the de-identified Optum Clinformatics® Data Mart (from 2016 to 2019). Two HK cohorts were identified: 1) pts exposed to PAT+RAASi therapy; and 2) pts who discontinued RAASi therapy (DC RAASi). All pts had serum K+ ≥5.0 mEq/l, HK diagnosis, and ≤6 mos insurance enrollment. Pts were propensity score matched on baseline characteristics. Relative healthcare spending rate (exposure contrast: PAT+RAASi vs DC RAASi [reference]) was analyzed at 3 mos using zero-inflated negative binomial regression. Cost outcomes included: total, inpatient, emergency department (ED), outpatient services, and outpatient pharmacy. Study cohorts included 464 pts (232 matched pairs). Overall, mean age was 74 yrs, 59% male, and 31% Hispanic. Pts had a mean of 5 comorbidities: CKD (95%), diabetes mellitus (73%), chronic heart failure (32%), cardiac arrhythmias (33%), and coronary artery disease (39%). At 3 mos, 168 pts (84 matched pairs) remained uncensored and were included. Total healthcare spending rate for DC RAASi cohort was $15,344 vs $9135 (95% confidence interval, $6303, $13,241) for PAT+RAASi cohort over 3 mos (P<0.01; Figure) and was driven by marked reductions in outpatient and ED costs.

**Conclusion**: Our data show that in WT mice during 0KD, activation of NCC was higher in KS-KO mice than in WT mice. KS-WNK1/4 modulation using a model to imitate what occurs in wild life. Thus, wild type mice are better suited to respond to extreme changes in potassium diet as those that probably occurs in wild life in mammals.

Funding: NIDDK Support, Government Support - Non-U.S.
TH-OR26

Dietary Anion Prioritizes Pendrin Activation over Aldosterone

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

Methods: C57/B16 male mice (2 month old) were randomized to matched control (2% KCl), high potassium bicarbonate (13.4% KHC03), or high potassium chloride (10% KCl) diets (4 days). A separate cohort of mice was randomized to a switch anion diet protocol, whereby mice were first adapted to the high KHC03 or high KCl diet (4 days), and the response to changing the anion in the context of high potassium, high aldosterone was assessed at 24 and 48 hours. Aldosterone and plasma electrolytes were measured by standard methods. Kidney Pendrin mRNA and protein abundance were assessed by qRT-PCR and western blot, respectively.

Results: Dietary KCl and KHC03 loading increased plasma potassium and aldosterone to the same extent but had opposite effects on pendrin abundance. KHC03 loading increased pendrin, while dietary KCl loading inhibited it. Pendrin protein and transcript abundance decreased within 24 hours of switching the high KHC03 diet to high KCl, and the response was coincident with an increase in plasma chloride and a decrease in bicarbonate. Switching the high KCl diet to high KHC03 had the opposite response, increasing pendrin protein and transcript as plasma bicarbonate increased and chloride decreased. Neither anion switch protocol changed the extent of hyperaldosteronism or hyperkalemia.

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

Funding: NIDDK Support, Private Foundation Support

TH-OR27

Intracellular Water Shift and Disturbed Osmoregulatory Responses toTH-OR27

High Sodium in Patients with Hereditary Multiple Exostosis


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

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

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

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

Funding: Commercial Support - Vifor Pharma, Inc.

TH-OR28

Renal Lymphatic Pumping Involves Intestinal Sodium Regulation of NKCC1 Transporter

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

Methods: Paroxymic anion contracepted injected rats (PAN) served as a model of natriuretic syndrome and saline-injected rats served as control. In vivo, MRI was used to assess the renal sodium and water content. Renal lymph, which reflects the interstitial composition, was collected and sodium concentration analyzed. Ex vivo, contractile dynamics of isolated renal collection lymphatic vessels were studied in a perfusion chamber. Stained LECs were used to assess high sodium environment and sodium concentration.

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

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

Funding: NIDDK Support

TH-OR29

A Novel Model of Hyperuricemia via Inducible Uricase Knock-Out

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

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Methods: CRISPR-Cas9 was used to insert LoxP sites into the Uox gene of C57BL/6J mice with either C57BL/6J or CD1 background. Cre (Gt(ROSA)26Sorcre/1Rorag) mice were generated using these CRE maps to induce the deletion of APOL1 exon 1 (APOL1+/-) and the loss of transcript but not protein. The effects on renal function were assessed by measuring blood pressure and urinary albumin excretion. Urinary albumin levels were quantified using a colorimetric assay.

Results: The deletion of APOL1 exon 1 resulted in a significant increase in urinary albumin excretion, indicating a potential role for APOL1 in mediating kidney disease.

Conclusions: These findings suggest that APOL1 may play a significant role in the development of kidney disease and that targeting APOL1 may be a promising therapeutic strategy for reducing the risk of kidney disease.

TH-OR32
Epistatic Interactions of APOL1 Modify the Association Between APOL1 and CKD in African and Hispanic Americans

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Background: Chronic kidney disease (CKD) is a major public health problem, and risk is increased in African American (AA) and Hispanic Americans (AAs). Prevalence of achieving the low-risk genotype was 14.1% for AA and 12.4% for AAs.

Methods: In this study, we conducted a genome-wide single nucleotide polymorphism (SNP)xAPOL1 interaction analysis to identify SNPs that modify the association of APOL1 high-risk genotypes with CKD in the largest minority cohort to date. Interaction analyses were conducted separately for four independent cohorts, 12,145 African Americans (AAs) and 16,580 Hispanic Americans (HAs) from the Population Architecture through Genomics and Environment Health (PAGE) Study and 6,827 AAs and 10,314 HAs from the BioMe Biobank, followed by sample size based meta-analysis.

Results: Among the four cohorts, CKD cases and APOL1 high-risk genotypes were observed with higher frequencies in AA (8.48% CKD and 11.95% APOL1 in PAGE, 18.21% CKD and 13.90% APOL1 in BioMe) than in HA (3.40% CKD and 0.45% APOL1 in PAGE, 14.14% CKD and 1.69% APOL1 in BioMe). We tested about 28 million SNPs in our interaction analyses and identified 51 significant SNPs (P value < 1.0 x 10^-8) interacting with the APOL1 locus across the genome (Figure 1). Of these, 28 SNPs were within a gene, and 14 of the 28 SNPs were within the gene PEPZP which has been shown to be involved in controlling translation and glucose homoeostasis.

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

TH-OR31
Deconvolution of Genetic Variation Using High-Quality cis-Regulatory Elements Map of Kidney Cells

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

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

Results: Our high-quality CRE maps have enabled us to detect >100,000 CREs for podocytes, a key (<1%) cell type involved in kidney filtration function. Newly found CREs explained the significant proportion of SNP-heteritability for a major kidney trait (Urinary Albumin-to-Creatinine Ratio (UACR); Pr[h^2]=9.3%). Heritability analysis using these CRE maps uncovered the differential contribution of specific cell types to two disease subphenotypes with distinct functional traits (e.g., glomerular filtration rate (GFR)). As would be predicted from physiologic understanding, CREs for podocytes and proximal tubule cells (PT) had enriched proportion of SNP-heteritability for UACR and eGFR, respectively (UACR; Pr[h^2]= 6.8 for podocyte, 2.3 for PT, eGFR; Pr[h^2]= 3.1 for podocyte, 4.3 for PT. Moreover, we found the podocyte relevance of a known GWAS variant (rs17831251; OR=2.2, P=4.7 x 10^-10) on PLZ121A associated with Membranous Nephropathy. Our CRE map showed strong podocyte-unique CRE that overlaps with the index variant, suggesting that the index SNP is potentially the causal variant perturbing podocyte-specific transcriptional regulation of PLZ121A.

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

Funding: NIDDK Support, Private Foundation Support

TH-OR33
Phenotypic Spectrum of COL4A3 Variants: The Geisinger Mycode/ DiscoEHR Study

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

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

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9
COL4A3 P/LP variants and Alport syndrome-related phenotypic features were assessed using logistic regression. Additional analyses were done comparing carriers and non-carriers for the most common variant (p.Gly695Arg) observed in our cohort.

**Results:** There were 329 (0.2%) participants with a previously reported P/LP rare COL4A3 variant. Individuals with a COL4A3 variant (mean age 58.8 years) were at increased risk of ESKD (OR 3.79, 95% CI: 2.36-6.08), hematuria (OR 1.99, 95% CI: 1.37-2.88), FSGS/renal sclerosis (OR 7.46, 95% CI: 3.31-16.84), and eGFR <60 ml/min/1.73m² (OR 1.46, 95% CI: 1.07-1.99) but not hearing loss. The most common P/LP variant was p.Gly695Arg with 161 heterozygous individuals in 58 families (Table). Compared to non-carriers, those with the p.Gly695Arg variant were at increased risk of hematuria (OR 3.44, 95% CI: 1.38-8.86), and ESKD (OR 12.39 (1.59-96.33; P=0.002). Two patients had a known family history of Alport Syndrome, and only 1 patient had been diagnosed using clinical genetic testing.

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

**Funding:** NIDDK Support

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**TH-OR34**

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

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

**Methods:** We applied the GenePy scoring system integrating patient zygosity, allele frequency, and deleteriousness metrics. We identified unrelated Europeans for a phenotype-genotype approach of 232 cases with TKD and 8,282 controls with no documented kidney disease. We then took an unbiased genotype-phenotype approach by calculating GenePy scores for all 78,050 germline genomes. Individuals were ranked by gene score, and individuals with the highest scores were assessed for their phenotype.

**Results:** The difference in top-decile scores between cases and the same proportion of controls was statistically significant for PKD2 (p=2.81x10⁻¹⁰), DNAJB11 (p=3.56x10⁻¹⁰), XPNPEP3 (p=0.0083), UMOD (p=0.0015) and CEP290 (p=0.034). Novel variants consistent with TKD were identified. The unbiased genotype-phenotype approach additionally revealed variants consistent with monogenic TKD in participants recruited for diverse reasons, including cancer.

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

**TH-OR35**

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

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

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

**Results:** We discovered (1) increased expression of APOL1 in HR and nine other significantly differentially expressed genes, including stanniocalcin (STC1), which has a role in mitochondrial and calcium-related processes, (2) differential correlations between HR and LR APOL1 and metabolism pathway genes, but similar correlations with extracellular matrix- and immune-related genes, (3) significant loss of co-expression of mitochondrial genes in HR FSGS, and (4) an NF-kB-down-regulating gene, NKRAS1, as the most significant hub gene with strong differential correlations with NDUF family and immune-related genes.

**Conclusions:** Overall, differences in mitochondrial gene regulation appear to underlie many differences observed between HR and LR FSGS. All data are available for secondary analysis through the “APOL1 Portal” (http://apol1portal.org).

**Funding:** NIDDK Support

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**TH-OR36**

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

Ludmila Cebotaru, Murali K. Yanda, Johns Hopkins University, Baltimore, MD.

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

**Methods:** We used a combination of MRI, Immunocytotyping and Immunostaining to test VX-809 in a slowly progressing RC/RC mouse model, bearing the R327TC mutation.

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

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

**Funding:** NIDDK Support

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**Underline represents presenting author.**
Cynthia
Common Pathomechanisms
Comparative PKD1 and PKD2 Missense Variant Profiling Aids
VX-809 shrinks the cysts between 6 and 8 months of age
that depicted here (6M-Control) was allowed to develop cysts slowly over 6 months and then
Fig 1: MRI images of mice kidneys Three sequential images are depicted. The animal
VUS pathogenicity, and highlight a continuum of allele penetrance across the
PKD1 and PKD2 Missense Variant Profiling Aids Common Pathomechanisms
Comparative PKD1 and PKD2 Missense Variant Profiling Aids Molecular Diagnoses Across the ADPKD Spectrum and Reveals
Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of fluid-filled renal cysts, often leading to kidney failure. Typically, monoallelic PKD1 or PKD2 variants cause ADPKD, however, complex inheritance and a broad phenotypic spectrum also exist. The advent of genomewide variant screening has emphasized the importance of ADPKD molecular diagnostic methods to reliably determine the pathogenicity of variants of unknown significance (VUS).
Methods: Here, we developed a cell-based flow cytometry assay to assess the pathogenicity of PKD1 and PKD2 VUS. This assay utilizes localization of polycystin 1 (PC1; encoded by PKD1) to the apical plasma membrane, where formation of the PC1/PC2 complex (PC2; encoded by PKD2) is required for proper PC1 trafficking. Employing this assay, we have assessed 48 PKD1 and 44 PKD2 variants with predicted pathogenicity ranging from fully penetrant monoallelic, to incompletely penetrant biallelic, and likely benign variants.
Results: The majority of likely pathogenic monoallelic PKD1 and PKD2 variants perturb PC1 trafficking by >80%, with a correlation between the predicted penetration (determined bioinformatically) and surface PC1. In cis monoallelic PKD1 variants have an additive effect and perturb PC1 trafficking by 60-98%, whereas proposed biallelic PKD1 variants exhibit variable impacts (60-70% perturbation; majority >60%). In contrast, likely benign variants have little or no impact. To understand mechanisms underlying aberrant PC1 trafficking, we evaluated defective protein folding under enhanced folding conditions (reduced culture temperature; 30°C). The majority of PKD1 and PKD2 monoallelic, and all PKD1 and PKD2 complex variants impact PC1 or PC2 folding, and can be partially or fully rescued at 30°C.
Conclusions: These studies describe a novel in vitro assay for determining PKD1 and PKD2 VUS pathogenicity, and highlight a continuum of allele penetrance across the ADPKD spectrum. This firmly establishes PC1 trafficking as a common PKD1/PKD2-mediated ADPKD pathomechanism, but suggests that other mechanisms account for a minority of variants. Further, demonstrated aberrant PC1 or PC2 folding suggests a role for chaperone therapy in ADPKD.
Funding: NIDDK Support

TH-OR38
The C-Terminal Tail of Polycystin 1 Rescues Cystic Phenotype in a Mitochondrial Enzyme-Dependent Fashion
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Background: Approximately 85% of Autosomal Dominant Polycystic Kidney Disease (ADPKD) cases are caused by mutations in PKD1, which encodes polycystin-1 (PC1). PC1 is a large transmembrane protein that underlies C-terminal cleavage, generating fragments (PC1-CTT) that translocate to mitochondria and nucleus. We find that PC1-CTT expression in an inducible PC1 KO ADPKD mouse model substantially rescues cystic phenotype and we elucidate mechanisms involved in this effect.
Methods: We generated BAC transgenic mice expressing a Flex-Stop 2HA-PC1-CTT inserted in the Rosa26 locus and crossed it with the inducible Pax6rtTA; TetO-Cre. Pkd1<sup>fl/fl</sup> ADPKD mouse model. Doxycycline induction of these mice (PC1-CTT; Pax6rtTA; TetO-Cre; Pkd1<sup>fl/fl</sup> on the C57BL/6J background) leads to PC1-CTT expression in renal epithelial cells that lack full-length PC1. We applied MS-based proteomics and Co-IP techniques to identify PC1-CTT interactors and used MS-based metabolomics to identify mitochondrial differences associated with the observed phenotype.
Results: Compared to PC1 KO mice, PC1 KO expressing PC1-CTT have 3-fold lower kidney weight/ body weight ratio (5.30% vs 14.85%, p<0.0001) and 3.6-fold lower BUN (32.7mg/dL vs 120.7mg/dL, p=0.0008), with both groups presenting comparable gender distributions. BUN levels in PC1-CTT-expressing ADPKD mice are comparable to those in WT controls. We show that PC1-CTT interacts with mitochondrial enzyme Nicotinamide Nucleotide Transhydrogenase (NNT) and confirm the importance of this interaction by crossing the same PC1-CTT expressing PC1 KO mice with NNT-deficient C57BL/6J mice. These mice do not exhibit an improved cystic phenotype. Both in vivo and in vitro, PC1-CTT re-expression in the presence of NNT leads to increased mitochondrial mass, altered redox modulation, increased assembly of ATP synthase at a “per mitochondria” level as well as decreased tubular proliferation, suggesting potential mechanisms for the observed rescue. Finally, unbiased metabolomics reveals that PC1-CTT’s ability to rescue the ADPKD metabolic profile is tied to the presence of NNT.
Conclusions: Expression of PC1-CTT and its interaction with NNT significantly rescues ADPKD renal phenotype. Considering its small size, PC1-CTT could be explored as a gene therapy approach for ADPKD.

Funding: NIDDK Support, Private Foundation Support

TH-OR39
Read-Through Therapeutics Reduce Cystogenesis in a Novel Cohort of CRISPR Base Edited ADPKD Organoids
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Background: In autosomal dominant polycystic kidney disease (ADPKD), truncating nonsense mutations are responsible for 40-50% of cases, with increased disease severity and limited treatment options. Eukaryotic ribosomal selective glycosides (ERSGs) allow read-through of premature stop codons to restore full-length proteins as a novel therapeutic approach. However, existing animal and kidney organoid models of ADPKD lack mutations amenable to read-through.
Methods: Human pluripotent stem cells were CRISPR base edited to introduce four specific nonsense mutations previously documented in ADPKD patients – PKD1 R243X and Q383X and PKD2 R186X and R872X. Mutations were confirmed by sequencing and protein changes by immunoblot. Mutant and isogenic control stem cells were differentiated into kidney organoids to determine if nonsense mutations conferred a cystic phenotype. Premature stop codon read-through potential was evaluated for impact on cyst formation and toxicity (live/dead staining and LDH release) over a period of two weeks using two unique ERSGs.
Results: Nonsense mutant clones of each targeted genotype were obtained with the desired single base pair mutation and lacked expression of full-length protein. Fewer than 5% of isogenic control organoids formed cysts compared to > 80% in untreated mutant organoids. Treatment of mutant organoids with ERSGs reduced cystogenesis to < 20% and slowed the rate of cyst expansion in a dose-dependent manner. Treatment associated toxicity was not significantly detected at efficacious doses.
Conclusions: CRISPR base editing enabled rapid generation of an ADPKD organoid cohort with patient targeted nonsense mutations. The data suggest that read-through by ERSGs is a viable therapeutic approach for reducing cystic burden in a large subpopulation of patients with ADPKD, supporting the advancement of ERSGs in human clinical trials.
Funding: NIDDK Support, Commercial Support - Eloxx Pharmaceuticals

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TH-OR41
Role of Hypertension in the Risk of Heart Failure in CKD
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Background: Chronic kidney disease (CKD) is a risk factor for heart failure (HF), but the extent to which hypertension (HTN) contributes to development of HF in CKD is unclear.

Methods: We used the VA Informatics and Computing Infrastructure (VINCI) platform to identify a national cohort of veterans with prevalent CKD (two or more outpatient CKD-EPI eGFR <60 ml/min/1.73m2) taken 60 days apart from January 2010 to December 2015. We used inpatient and outpatient ICD 9/10 codes to define HF admissions and incident HF through August 2018. We first related CKD stages at baseline with the time to HF hospitalizations and incident HF with adjustment for demographics and baseline comorbidity in a multivariable Cox regression. Next, we adjusted for baseline blood pressure (BP) and BP-lowering medications (BP meds). Finally, we conducted a time varying Cox regression model with 3-month averages of BP values and BP meds.

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

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

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

TH-OR40
Whole-Genome Sequencing Reveals the Genetic Architecture of Posterior Urethral Valves
Melanie Posterior Urethral Valves Whole-Genome Sequencing Reveals the Genetic Architecture of Posterior Urethral Valves
Melanie M. Chan,1 Omid Sadeghi-Alavijeh,1 Horia Stanescu,1 Stefanie Weber,2 Alina Hilger,3 Adrian S. Wooll,7 William G. Newman,3 Detlef Bockenhauer,4,6 Adam P. Levine,1 Daniel P. Gale,1 Genomics England Research Consortium 1University of Manchester Faculty of Biology Medicine and Health, Manchester, United Kingdom; 2Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.

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

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

Results: Exome-wide there was no significant enrichment of rare coding variation in any one gene. SV analysis identified an increased burden of rare variations affecting CTCF-only cis-regulatory elements (P=2.0x10^-8; OR 2.1), but these did not affect any single genomic locus recurrently. GWAS of 17 million variants with minor allele frequency (MAF) > 0.001 revealed significant (P<5x10^-7) associations at two loci: 12q24.23 (P=7.8x10^-12; OR 4.4; MAF 0.007) and 12q24.21; OR 2.1), but these did not affect any single genomic locus recurrently. GWAS of 17 million variants with minor allele frequency (MAF) > 0.001 revealed significant (P<5x10^-7) associations at two loci: 12q24.23 (P=7.8x10^-12; OR 4.4; MAF 0.007) and 12q24.21 (P<2.0x10^-8; OR 7.2; MAF 0.007), both of which replicated in an independent cohort of 398 European PUV patients. Bayesian fine mapping and in silico functional annotation mapped these loci to the transcription factor TBX5 and planar cell polarity gene PTK7, respectively. Both are highly expressed in the embryonic mouse urethra and known to regulate development.

Conclusions: This work demonstrates that non-specific perturbations of broad regulatory networks and chromatin looping may be important in the pathogenesis of embryonic mouse urethra and known to regulate development.

TH-OR42
Prediction of Incident Heart Failure in CKD
Leila R. Zelnic,1 Michael Shlipak,3 Elsayed Z. Soliman,8 Amanda H. Anderson,2 Robert Christenson,10 Mayank Kansal,9 Rajat Deo,3 Jiang He,2 Bernard G. Jaar,14 Matthew R. Weir,10 Pandurangu S. Rao,3 Debbie L. Cohen,3 Jordana B. Cohen,14 Harold I. Feldman,14 Alan S. Go,4 Nisha Bansal,2 University of Washington, Seattle, WA; Tulane University, New Orleans, LA; University of Pennsylvania, Philadelphia, PA; Johns Hopkins University, Baltimore, MD; University of Michigan, Ann Arbor, MI; Kaiser Permanente Northern California, Oakland, CA; University of California San Francisco, San Francisco, CA; Wake Forest University, Winston-Salem, NC; University of Illinois at Chicago, Chicago, IL; University of Maryland School of Medicine, Baltimore, MD.

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

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

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

Jason Chung,1 Andrew Yu,4 Abdulaziz A. Bamhrnaz,2 Joycelyn E. Ewusie,3 Arjun K. Pandey,1 Mark Mitsnefes,4 Rulan S. Parekh,1 Janis M. Dione,1 Rahul Chanchlani.1 2University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; 3McMaster Children’s Hospital, Hamilton, ON, Canada; 4BC Children’s Hospital, Vancouver, BC, Canada; 5McMaster University, University of Alberta Faculty of Science, Edmonton, AB, Canada; 6McMaster University, Hamilton, ON, Canada; 7Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 8The Hospital for Sick Children, Toronto, ON, Canada; 9The Research Institute of St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada.

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

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

Results: Of 8996 studies, 38 were included for analysis. SCO indices were correlated directly with renal dysfunction (Fig.A). Myocardial mitochondrial damage did not correlate with blood pressure but correlated directly with renal dysfunction (Fig.B). Myocardial mitochondrial damage and preserves cardiac function in renovascular hypertension (RVH), but its effect on the biological mechanisms implicated in cardiac damage remains unknown. We hypothesized that restoration of kidney function by PTRA ameliorates myocardial mitochondrial damage and preserves cardiovascular function in pigs with metabolic syndrome (MetS) and RVH.

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

Funding: NIDDK Support

Hypertension and Cardiovascular Risk in CKD

Hypertension and Cardiovascular Risk in CKD

TH-OR43

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

Jason Chung,1 Andrew Yu,4 Abdulaziz A. Bamhrnaz,2 Joycelyn E. Ewusie,3 Arjun K. Pandey,1 Mark Mitsnefes,4 Rulan S. Parekh,1 Janis M. Dione,1 Rahul Chanchlani.1 2University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; 3McMaster Children’s Hospital, Hamilton, ON, Canada; 4BC Children’s Hospital, Vancouver, BC, Canada; 5McMaster University, University of Alberta Faculty of Science, Edmonton, AB, Canada; 6McMaster University, Hamilton, ON, Canada; 7Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 8The Hospital for Sick Children, Toronto, ON, Canada; 9The Research Institute of St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada.

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Funding: NIDDK Support

Hypertension and Cardiovascular Risk in CKD

Hypertension and Cardiovascular Risk in CKD

TH-OR44

Hypertension and Cardiovascular Risk in CKD

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

Methods: Pigs were studied after 16 weeks of MetS+RVH, MetS+RVH treated 4 weeks earlier with PTRA, and Lean and MetS Sham controls (n=6 each). Cardiac and renal function was assessed by multi-detector CT, whereas cardiac mitochondrial function and function, and angiography were assessed by 13C-Metabolism PET.

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

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

Funding: NIDDK Support

Hypertension and Cardiovascular Risk in CKD

Hypertension and Cardiovascular Risk in CKD

TH-OR45

Hypertension and Cardiovascular Risk in CKD

Background: A linear relationship exists between systolic blood pressure (SBP) and cognitive impairment in patients with chronic kidney disease (CKD). We therefore sought to investigate the relationship between SBP and cognitive impairment in patients with CKD.

Methods: Using data from the Chronic Renal Insufficiency Cohort Study, we investigated the association between baseline and time-updated SBP and incident cognitive impairment, defined as a decline of 3MS score > 8 points from 2004 to 2012. We used discrete hazards models that adjusted for demographics as well as cardiovascular and kidney disease risk factors.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: Mean (SD) age and eGFR (SD) by the CKD-Epi equation of the 3753 participants were 58 years (11), and 44 mL/min/1.73m² (15), respectively. Baseline cognitive impairment was present in 10.1% of overall participants (n = 365), and 5.4%, 9.5%, and 16.4% of participants with baseline SBP <120, 120-140, and ≥140 mm Hg, respectively (p < 0.01). There were 314 individuals who developed cognitive impairment during a median 6 years of follow-up. After multivariable adjustment, participants with higher baseline SBP were more likely to have incident cognitive impairment (hazard ratio (HR) [95%CI] = 1.09 [1.03, 1.16]) per 10 mmHg higher SBP; this relationship was attenuated when using time-updated SBP (HR [95%CI] = 1.04 [0.99, 1.09]) (Table 1).

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

Funding: NIDDK Support

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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Unadjusted HR (95% CI)</th>
<th>Model 1*</th>
<th>Model 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≤120 mmHg</td>
<td>0.90 (0.80, 1.03)</td>
<td>0.90 (0.80, 1.03)</td>
<td>0.90 (0.80, 1.03)</td>
</tr>
<tr>
<td>SBP &gt;120 mmHg</td>
<td>0.92 (0.75, 1.13)</td>
<td>0.92 (0.75, 1.13)</td>
<td>0.92 (0.75, 1.13)</td>
</tr>
<tr>
<td>Time-updated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≤120 mmHg</td>
<td>0.90 (0.76, 1.06)</td>
<td>0.90 (0.76, 1.06)</td>
<td>0.90 (0.76, 1.06)</td>
</tr>
<tr>
<td>SBP &gt;120 mmHg</td>
<td>0.93 (0.79, 1.09)</td>
<td>0.93 (0.79, 1.09)</td>
<td>0.93 (0.79, 1.09)</td>
</tr>
</tbody>
</table>

n = 25,227, after excluding individuals with cognitive impairment at baseline and those missing blood pressure measurements.

**Adjusted for age, sex, race, education, cardiovascular disease, stroke, body mass index, diabetes mellitus, and other comorbidities.

*Adjusted for age, sex, race, education, cardiovascular disease, stroke, body mass index, diabetes mellitus, and other comorbidities.

TH-OR46

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

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

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

Results: Mean age was 68.9 years, 35% were women and 66% White. There were 640 MCI/PD events over 39,022 participant-years. Compared to standard SBP, intensive SBP control further lowered the DBP in those in the lowest baseline DBP tertile (Figure 1A) but also lowered the risk of MCI/PD (Table 1). While lower baseline DBP was associated with higher risk of MCI/PD (Table 1), there was no evidence that intensive SBP lowering increased the risk of MCI/PD in those with low baseline DBP (Table 1B) and with baseline DBP x SBP goal interaction p = 0.37.

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

Funding: Other NIH Support - NIA

Table 1: Compliance at Baseline and Endpoint

<table>
<thead>
<tr>
<th>Compliance (mmHg)</th>
<th>Baseline (Mean, SD)</th>
<th>Endpoint (Mean, SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group</td>
<td>1.6 (0.7)</td>
<td>2.0 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control Group</td>
<td>1.5 (0.5)</td>
<td>1.7 (0.5)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Table 2: Compliance at Baseline and Endpoint

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
TH-OR48
Regulation of Sodium Excretion and Blood Pressure by the Nuclear Factor of Activated T Cells 5 (NFAT5) in Renal Tubular Cells
Akiko Hiramatsu, Yuichiro Izumi, Yutaka Kakizoe, Masataka Adachi, Hiroshi Nonoguchi, Takashige Kuvabara, Masashi Mukoyama, Department of Nephrology, Kumamoto University, Graduate School of Medical Sciences, Kumamoto, Japan.

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

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

Results: Compared to WT mice, KO mice exhibited polyuria (WT vs. KO: 2.0 ± 0.08 vs. 5.2 ± 0.18 ml/day) at basal condition. The serum sodium level was increased (151.8 ± 0.78 vs. 156.6 ± 0.45 mmol/L) and the urinary sodium excretion was decreased (498.7 ± 25 vs. 368.9 ± 15 mmol/g creatinine) in KO mice. Interestingly, the systolic blood pressure was significantly increased in KO mice (WT: 114.9 ± 1.1 mmHg vs. KO: 145.1 ± 1.1 mmHg). The expression of AQP2 and UT-A1, a water channel and a urea transporter, respectively, was increased in KO mice fed HSD compared to WT mice fed HSD. ENaC protein levels were increased in KO mice fed HSD compared to WT. The urea concentration was lower and the Na concentration was higher in the medulla of KO mice than those of WT mice. HSD significantly increased the medullary Na concentration, but not the urea concentration in KO vs. WT mice fed HSD.

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

Funding: Government Support - Non-U.S.

TH-OR49
Fluid Overload, 24-Hour Blood Pressure Patterns, and Their Association with Cardiovascular and Kidney Outcomes in CKD
Ye Fun Ko1, Jong Hyun Hee2, Tae-Hyun Yoo,1,3 Yonsei University College of Medicine, Seoul, Republic of Korea; 2Gangnam Severance Hospital, Gangnam-gu, Seoul, Republic of Korea; 3Yonsei University Institute of Kidney Disease, Seodaemun-gu, Seoul, Republic of Korea.

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

Methods: A total of 1,147 CKD (stage 1 to 5) patients were enrolled from the prospective observational cohort of CMERC-III (Cardiovascular and Metabolic Disease Etiology Research Center-High Risk). The patients were classified into tertile based on fluid status defined as the extracellular water to total body water ratio (ECW/TBW) measured by bioelectrical impedance analysis; dipper (nighttime BP fall >20%), nondipper (nighttime BP fall 0-10%), and reverse diper (nighttime BP fall >10%). Primary outcome was composite of nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality. The secondary outcome was progression of CKD (composite of at least 50% decrease in eGFR -50% from baseline or eGFR <60 ml/min/1.73 m², or end-stage kidney disease).

Results: The mean age of study subjects was 59.9±12.2 years and 615 (53.6%) were male. The hypertensive group was associated with increased risk of reverse-dipping pattern (OR, 2.46; 95% CI, 1.30-4.64; P=0.01). During a median follow-up of 42.1 (41.3-42.9) months, the composite of cardiovascular events and CKD progression occurred in 42 (3.7%) and 345 (30.1%), respectively. The Kaplan-Meier analysis showed that compared with dipper, the nondipper was associated with increased risk of cardiovascular events and CKD progression compared to hypovolemic group. In multivariable Cox analyses, hypervolemic group was associated with increased risk of cardiovascular events (HR, 4.44; 95% CI, 1.16-17.0; P=0.03). Moreover, hypertensive group was associated with increased risk of CKD progression (HR, 2.47; 95% CI, 1.77-5.45; P=0.001). This increased risks of cardiovascular events and CKD progression with hypertensive status were still consistent in patients with reverse-dipping pattern.

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

TH-OR50
Galectin 3 and Air Pollution in Hypertensive Patients with and Without CKD
Hafsa Tarai,1,2 Sadect Al-Kindi,1,2 Mahboob Rahman,1,2 Jackson T. Wright,1,2 Sanjay Rajagopalan,1,2 Mirela A. Dobrea,1,2,3 University Hospitals, Cleveland, OH, 1Case Western Reserve University, Cleveland, OH.

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

Methods: Satellite-derived PM2.5 measurements were linked with participants in the Systolic Blood Pressure Intervention Trial (SPRINT, Clinicaltrials.gov NCT01206002). A total of 1019 SPRINT participants with available Galectin 3 levels at study baseline and 24 months follow-up were included in these analyses. Multivariable linear regression models, adjusted for age, sex, race, eGFR, Framingham risk score, body mass index, and randomization assignment with fully to examine the association between air pollution and Galectin 3 at baseline and longitudinal change at 2 years.

Results: The mean PM10 was 9.6 μg/m³, and the median (IQR) Galectin 3 level was 14.4 (11.5-18.0) ng/mL. In multivariable models, we found no association between PM10 and baseline (β=-0.02, P=0.46) or longitudinal change (β=0.05, P=0.12) in Galectin 3. In the subgroup of participants with CKD (n=201), PM10 was associated with change in Galectin 3 (β=-0.21, P=0.002), which remained statistically significant after multivariable adjustments (β=-0.23, P=0.003). In the overall cohort (n=1019), there was a significant interaction between PM10 and eGFR with change in Galectin 3 (p-value for interaction=0.02), (Figure).

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

Funding: Other NIH Support - MD is supported by R01HL141846
between AMR and No AMR Cases (AUC 0.8742, 95% CI 0.8095-0.9388, p<0.0001) and we developed a gene score cut-off, maximising sensitivity and specificity.

In biopsies suspicious for AMR, but which did not complete the full diagnostic criteria, a high Gene Score was predictive of allograft loss, compared to biopsies with a low gene score (p=0.0065).

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

TH-OR52

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

Serpi Clotet Freixas, Catriona M. McEvoy, Chiara Pantrello, Max Kotlyar, Madhurangi Arambewela, Alexander Boshart, Sofia Farkoma, Yun Niu, Yanhong Li, Andrzej Chruscinski, Rohan John, Ana Konvalinka. University Health Network, Toronto, ON, Canada.

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

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

Results: We found 107 glomerular and 112 tubulointerstitial proteins significantly differentially expressed in AMR vs. ACR. Similarly, 112 (glomeruli) and 124 (tubulointerstitium) proteins were regulated in AMR vs. ATN. Basement membrane and extracellular matrix (ECM) proteins were decreased in both compartments in AMR, compared with ACR and ATN. We verified decreased glomerular and tubulointerstitial LAMC1 expression, and decreased glomerular NPHSL1 and PTPP4R expression in AMR. Cathepsin-V (CTSV) was predicted to cleave ECM-proteins in the AMR glomeruli. We identified galectin-1, an immunomodulatory protein upregulated in AMR glomeruli and tubulointerstitium, which together with interferon gamma and tumor necrosis factor-alpha (TNFα), trigger graft failure. The reasons behind cell-specific injury in AMR remain unclear. Identifying compartment-specific proteome alterations may help uncover mechanisms of early antibody-mediated injury.

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

TH-OR53

Single-Cell Profiling Reveals Sex-Based Transcriptional Programs in Kidney Transplantation: Breakthroughs from Basic to Translational to Clinical Research

Garrett M. Wang, Gary McEvoy,1,2 Mehran An,1,2 Sofia Pastrello,1,2 Konvalinka.1,2

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

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

Results: 27677 high-quality cells forming 23 clusters were identified with several immune populations and all anticipated parenchymal populations. Individual kidney populations were examined for separation due to donor sex, with clear separation observed for the PT population alone using varimax-rotated principal component analysis (Fig1a).

Machine learning identified the most discriminant subset of genes (Model1: 80 genes) that could correctly classify cell sex (AUC 0.98). 75 genes were differentially expressed between males and females (p-value <0.05, LogFC>0.25). Anti-oxidant metallothionein genes were increased in females. Pathway analysis revealed metabolism-related processes (oxidative phosphorylation, and the TCA cycle) as increased in males (Fig1B).

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

TH-OR54

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

John Y. Choi,1,2 Hye-jung Kim,1,2 Harvey Cantor,3,2 Jamil R. Azzi,1,2 Brigham and Women's Hospital Department of Medicine, Boston, MA; ‘Harvard Medical School, Boston, MA; 1 Dana Farber Cancer Institute, Boston, MA.

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

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

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

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

Funding: Other NIH Support - NIAID

TH-OR55

Sodium-Glucose Cotransporter 2 Inhibitors in Kidney Transplant Recipients

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Background: The effect and safety of sodium-glucose cotransporter 2 inhibitors (SGLT2I) have not been investigated in kidney transplant recipients (KTRs) with diabetes. We evaluated the impact of SGLT2i in a multicenter cohort of diabetic KTRs.

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

Results: During the mean follow-up of 62.9 ± 42.2 months, the SGLT2i group had a lower risk of primary composite outcome than the control group in the multivariate and propensity score-matched models (Figure 1; adjusted hazard ratio [aHR], 0.52; 95% confidence interval [CI], 0.29–0.94; P = 0.031 and aHR, 0.46; 95% CI, 0.24–0.89; P = 0.022, respectively). Multivariate analyses consistently showed a decreased risk of serum creatinine doubling in the SGLT2i group. The overall eGFR remained stable without the initial dip after SGLT2i use. A minority (15.6%) of the SGLT2i users showed...
acute eGFR dip during the first month, but the eGFR recovered thereafter (Figure 2). The risk factors for the eGFR dip were time from transplantation to SGLT2i usage and mean tacrolimus trough level.

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

Figure 1. Kaplan–Meier curves for the outcomes

Figure 2. Temporal changes in the eGFR of SGLT2i users due to eGFR dip.

TH-OR56
The Role of Combined Gene Expression Profiling and Donor-Derived Cell-Free DNA to Diagnose Acute Rejection in Patients with Acute Allograft Dysfunction
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Background: Gene expression profiling (GEP) has been used to monitor for subclinical acute rejection. Conversely, the majority of data with donor-derived cell-free DNA (dd-cfDNA) has been in patients with allograft dysfunction. We hypothesized that combining GEP and dd-cfDNA could improve the diagnostic performance to detect acute rejection in patients with acute allograft dysfunction.

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

Results: Of 131 blood samples, 50 and 81 cases were biopsy-proven clinical acute rejection respectively. In binary analysis, GEP showed a lower positive predictive value (PPV) at 0.54 to 0.64 from dd-cfDNA, but a higher negative predictive value (NPV) at 0.80 to 0.70. When both tests were positive, PPV increased to 0.68 (95% CI, 0.50-0.88). In cases when both tests were negative, NPV increased to 0.88 (95% CI: 0.78-0.96) (Table 1). Performance of GEP and dd-cfDNA on detection of antibody-mediated rejection and acute cellular rejection shown in Figure 1. The combined use of two assays showed similar AUROC, to 0.75 than GEP (0.74, p-value = 0.26) and dd-cfDNA (0.72, p-value=0.69).

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

Funding: Commercial Support - Viracor-Eurofins

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-OR58

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

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

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

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

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

Funding: NIDDK Support

TH-OR59

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

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

Methods: A total of 6,581 donors and 13,350 controls were extracted from the national health insurance database between 2001 and 2018. Subjects took national health check-up 2 times and more were included. Controls were randomly extracted after matching with age, sex, date of donation, underlying hypertension and diabetes in the general population. Exposure to overweight and obesity was defined by body mass index (BMI) ≥23 kg/m2 and ≥25 kg/m2 during follow-up period. Overweight/obesity status was divided into 4 groups: 1) persistently no exposure, 2) exposure at only last health check-up, 3) persistently exposure in two times of health check-up, and 4) recovered from exposure at last health check-up. We used a multivariate logistic regression model to identify risk factors for new-onset hypertension.

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

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

TH-OR60

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

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Background: There is an inadequate supply of kidneys for transplant. The kidney donor profile index (KDP1) combines donor factors into a percentile that summarizes the likelihood of deceased donor transplant failure. High KDP1 kidneys are frequently discarded. Pre-emptive transplantation is associated with improved patient and graft survival, but it is unknown if this benefit is preserved with high KDP1 kidneys.

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

Results: Pre-emptive transplantation was associated with improved outcomes of ACGL, DCGL, and DWF (Fig 1). These results were consistent in the subgroup where the donor kidney was transplanted pre-emptively (before the recipient required dialysis) from a KDPI >= 91% donor (HR: 1.65, CI: 1.51 – 1.81) was similar to the risk of ACGL from a non-pre-emptive transplant from a KDPI 51-80% donor (HR: 1.57 CI: 1.48 – 1.66) (Fig 2).

Conclusions: In this mate kidney analysis, outcomes after a pre-emptive transplant were superior compared to a non-pre-emptive transplant, even among kidneys from donors with very high KDP1. Pre-emptive transplantation of high KDP1 kidneys is an opportunity to safely increase the number of kidney transplants from the limited supply of deceased donor kidneys.
TH-OR61
Quantifying Individual-Level Uncertainty in GFR Estimation
Xiaojian Zhu,1 Seth Lirette,1 Andrew D. Rule,2 Tom Mosley,1 Kenneth R. Butler,1 Javed Butler,1 Michael Hall,1 Pradeep Vaitla,1 James J. Wynn,1 Neville R. Dossabhoy,1 Eliseo Guallar,2 Tariq Shaﬁ,2 The University of Mississippi Medical Center, Jackson, MS; 2Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 3Mayo Clinic Minnesota, Rochester, MN.

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

Methods: Using data from four US community-based cohorts with mGFR (total N=3,223), we calculated eGFR from serum creatinine alone (eGFR CR), and cystatin and creatinine (eGFR CYS-CR) using the CKD-EPI equations without race coefﬁcients. Using quantile regression, we assessed eGFR’s individual-level reliability by calculating a 95% prediction interval (PI), deﬁned as the distribution of 95% of the observed mGFR values at a given eGFR. We also assessed eGFR’s population-level reliability using standard metrics, including median difference (eGFR-mGFR). All GFR results are presented as ml/min/1.73m².

Results: The participants’ median age was 61 years, 52% were Black, and 55% were female. The median mGFR was 68 (IQR: 46 to 88). At the population level, the median difference between eGFR CR and mGFR was small (1.4; 95% CI: 0.9 to 1.9). In contrast, the individual-level 95% PI of the eGFR CR was large, ranging from 53 to 120 at eGFR CR <60 and from 19 to 55 at eGFR CR >30 (Figure and Table). Substantial individual misclassiﬁcation was also noted using eGFR CR, 10% of individuals with eGFR CR >60 and 28% of those with eGFR CR <30 had mGFR above those thresholds. Results were similar for eGFR CYS-CR.

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

Funding: Other NIH Support - NINR, NHLBI

Table 1

<table>
<thead>
<tr>
<th>eGFR, mGFR</th>
<th>mGFR, ml/min/1.73m²</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>CYS-CR</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% Prediction Interval</td>
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<td>30-40</td>
<td>30-40</td>
</tr>
<tr>
<td>CR</td>
<td>CYS-CR</td>
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<tr>
<td>95% CI</td>
<td>95% Prediction Interval</td>
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<tr>
<td>30-40</td>
<td>30-40</td>
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TH-OR62
Kidney Function Biomarkers Among American Indians (AI) and Hispanic Americans (HA)
Monica Moya Balasch,1 Christos Argyropoulos, Maria-Eleni Roumelioti. University of New Mexico School of Medicine, Albuquerque, NM.

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

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

Results: Cohort consisted of 172 individuals, 61% female, 30.2% AI, 54.7% HA, age 51 ± 18, SBP/DBP 128 ± 14.7/77 ± 11.5 mmHg, Heart Rate 1.7 ± 0.1, BMI 20 ± 5, BUN 14 ± 5, SCr 0.9 ± 3.3, B2M 1.8 ± 0.5, CysC 0.7 ± 0.2, UACR 43.8 ± 231 mg/g, hs-CRP 4.8 ± 6.7 mg/L, HbA1c ± 1.7%. B2M was not associated with race/ethnicity/anthropometrics. CysC had the most non-kidney determinants [Table]. 75% of all log10 transformed values clustered together [Figure, yellow]. Ethnicity (p=0.02), HbA1c (p=0.03), hs-CRP (p=0.04) predicted discordance among the biomarkers (mauve).

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

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

Predictors of kidney biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Correlation Coefﬁcient</th>
<th>Signiﬁcance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr</td>
<td>-0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>B2M</td>
<td>-0.74</td>
<td>0.001</td>
</tr>
<tr>
<td>CysC</td>
<td>0.69</td>
<td>0.001</td>
</tr>
<tr>
<td>UACR</td>
<td>0.72</td>
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</tbody>
</table>

TH-OR63
Decline in Estimated Glomerular Filtration Rate (eGFR) Among Black Veterans After Removing the Race Coefﬁcient: Results of the US Veterans Health Administration Electronic Health Records
Guoafen Yang,1 Keith C. Norris,² Robert Nee,³ Julia J. Scialla,² Nan Hu,² Wei Yu,² Tom Greene,³ Alfred K. Cheung,4,5 University of Virginia School of Medicine, Charlottesville, VA; 4University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 5Walter Reed National Military Medical Center, Bethesda, MD; 6Florida International University, Miami, FL; 7University of Utah Health, Salt Lake City, UT; 8VA Salt Lake City Health Care System, Salt Lake City, UT.

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

Methods: eGFRs were calculated from serum creatinine measurements (excluding acute care settings) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) and the CKD-EPI without the race coefﬁcient (CKD-EPI-RACEout). We estimated eGFR slopes using quarterly averages of eGFRs for up to 8 years or until May 31, 2018 starting from the ﬁrst quarter after CKD incidence (i.e., first eGFR<60 mL/min/1.73m² for >3 months). We used linear mixed-effects models with random intercept and slope, adjusting for age, sex, eGFR at CKD incidence, and CKD incidence year.

Results: From 2003-2017, 139,921 Black veterans had incident CKD deﬁned by CKD-EPI-RACEout and 100,510 by CKD-EPI; and 636,598 White veterans by CKD-EPI, with median number of quarterly averages of eGFRs per patient of 8, 8, and 7, respectively. Overall, eGFR decline was greater among Blacks deﬁned by CKD-EPI than Whites (-1.37 vs. -0.84 mL/min/1.73m² per year, Table), consistent with prior ﬁndings. eGFR decline among Blacks by CKD-EPI-RACEout was attenuated (-1.07), but still greater than among Whites. In the two youngest groups, Blacks by CKD-EPI-RACEout still had about 2-fold larger decline versus Whites (Table).

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

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

<table>
<thead>
<tr>
<th></th>
<th>Black, eGFR defined by CKD-EPI</th>
<th>Black, eGFR defined by CKD-EPI without race coeff.</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-0.25 (±0.18,-0.32)</td>
<td>-0.18 (±0.15,-0.21)</td>
<td>-0.09 (±0.05,-0.14)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Under 45</td>
<td>45-49</td>
<td>50-54</td>
</tr>
<tr>
<td>age (years)</td>
<td>0.10 (±0.02, 0.18)</td>
<td>-0.14 (±0.12, -0.16)</td>
<td>-0.10 (±0.11, -0.16)</td>
</tr>
<tr>
<td>Age 50-64</td>
<td>0.71 (±0.32, 1.14)</td>
<td>0.37 (±0.21, 0.57)</td>
<td>0.22 (±0.14, 0.33)</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>0.84 (±0.33, 1.24)</td>
<td>0.45 (±0.25, 0.68)</td>
<td>0.26 (±0.17, 0.42)</td>
</tr>
<tr>
<td>Age 75-84</td>
<td>0.96 (±0.35, 1.36)</td>
<td>0.50 (±0.30, 0.78)</td>
<td>0.30 (±0.22, 0.47)</td>
</tr>
<tr>
<td>Age 85-94</td>
<td>1.09 (±0.37, 1.49)</td>
<td>0.60 (±0.39, 0.91)</td>
<td>0.38 (±0.30, 0.55)</td>
</tr>
</tbody>
</table>

TH-OR65

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

Chi-yuan Hsu,1,4 Wei Yang,1 Rishi V. Parikh,4 Amanda H. Anderson,2 Teresa K. Chen,3 Debbie L. Cohen,4 Jiang He,5 Madhumita J. Mohanty,6 James P. Lash,7 Katherine T. Mills,7 Anthony N. Muiru,8 Ashfin Parsa,10 Mildra M. Saunders,10 Tariq Shafi,9 Raymond R. Townsend,3 Sushrut S. Waikar,4 Jianqiao Wang,8 Myles Wolf,7 Thida C. Tan,10 Harold I. Feldman,10 Alan S. Go.11

CRIC1 University of California San Francisco, San Francisco, CA; 2Tulane University, New Orleans, LA; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Kaiser Permanente Northern California, Oakland, CA; 5University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 6University of Illinois at Chicago, Chicago, IL; 7The University of Mississippi Medical Center, Jackson, MS; 8Boston University School of Medicine, Boston, MA; 9Wayne State University, Detroit, MI; 10National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 11The University of Chicago Medicine, Chicago, IL; 12Duke University, Durham, NC.

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

**Methods:** We studied 1984 Chronic Renal Insufficiency Cohort (CRIC) Study participants with urinary 125I-iothalamate clearance GFR (iGFR) measurements and complete data on self-reported race, genetic ancestry, serum creatinine (SCr) & cystatin C. Genotyping was conducted using the Illumina HumanOmni1-Quad v1.0 microarray. The cohort was split into development (2/3) and validation (1/3) samples. Using linear regression, we derived GFR estimating equations for iGFR using SCr or cystatin C, age, sex, and self-reported race or African ancestry. The derived equations were then applied to the validation sample. Equation performance was assessed using root mean squared error (RMSE), adjusted R2 coefficient (R2), bias (iGFR - eGFR), and proportion of eGFR within 10% (P10) and 30% (P30) of iGFR.

**Results:** 539 participants were female and 458 self-identified as Black. Mean±SD age was 55.9±12.1 yr, iGFR 84±20 ml/min/1.73m2, median [IQR] SCr was 1.5 [1.1, 2.0] mg/dL, cystatin C 1.35 [1.09-1.71] mg/L. Median % African ancestry was 82.6% [74.5-88.3%] among those who self-identified as Black and 0.2% [0.1-2.0%] in those who did not. When using SCr to estimate GFR, incorporating vs omitting self-reported race yielded better performing estimates (Table). Incorporating genetic ancestry provided estimates of GFR similar to those incorporating self-reported race. Incorporation of race or ancestry was unnecessary when estimating GFR using cystatin C. A GFR estimating equation using cystatin C, age and sex performed comparably to an equation using SCr, age, sex, and race or ancestry.

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

**Funding:** NIDDK Support

TH-OR66

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

Anthony N. Muiru,1 Erin Madden,2 Michael Shlipak,3 Michelle M. Estrella,1 NA-ACCORD1 University of California San Francisco, San Francisco, CA; 2Northern California Institute for Research and Education, San Francisco, CA.

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

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

**Results:** 31,298 PWH were Black, in whom baseline antiretroviral use and HIV suppression were less prevalent and hepatitis C infection, hypertension and diabetes were more prevalent compared with White participants (N=27,542). eGFR without the race coefficient reclassified 25% of Black PWH into a worse CKD stage at baseline. Those reclassified had a higher prevalence of CKD risk factors compared with Black PWH who were not reclassified. When modeled with the race coefficient, Black PWH had 23% lower risk of progressing from CKD stage 1 to 2, similar risk of progressing from stages 2 to 3 and 3 to 4, and reduced risk of progressing from stage 4 to death or White PWH. When CKD progression was modeled using race-free eGFR, Black PWH consistently had a higher risk of CKD progression compared with White PWH (Table).
Conclusions: Prior studies suggesting that Black PWH have lower risk than White individuals for early CKD progression but higher risk at later stages were likely biased by the race coefficient. Assigning higher kidney function for all Black individuals on race systematically masks a subgroup of Black PWH who are at higher risk of CKD progression.

Funding: NIDDK Support

TH-OR67

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

Francesco Trevisani,1 Giulia Pegoraro,2 Daniele Pugno,2 Giulia Quattrini,1 Federico Di marco,3 Alessandra Cinque,1 Arianna Bettiga,1 Umberto Capitanio,1 Andrea Salonia,1 Giorgio Pizzagalli,1 Francesco Montouris.1 IRCCS Ospedale San Raffaele, Milano, Italy; 2Biorex S.R.L., Milano, Italy.

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

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

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

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

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

TH-OR68

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

Gregory L. Hundemer,1 Navdeep Tangri,2 Manish M. Sood,1 Ayub Akbari,1 1Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2University of Manitoba, Winnipeg, MB, Canada.

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

Methods: All patients referred to the advanced CKD clinic at the Ottawa Hospital from 2010-2018 were divided into age quartiles: <58, 58-67, 68-77, and ≥78 years. The study outcome was a single eGFR measure < 45 ml/min as study outcomes.

Results: The mean (SD) age and eGFR were 66 (15) years and 17 (6) mL/min/1.73 m2. The median (IQR) 2- and 5-year KFRE scores were 45% (22-64%) and 81% (55-96%), respectively. The KFRE overestimated the risk of kidney failure among the oldest age quartile (≥78 years) with absolute differences of 5.8% (P=0.01) and 21.6% (P<0.001) between predicted and observed risks over 2- and 5-years, respectively. The 2-year KFRE discrimination was reduced among patients ≥78 years compared with patients 58-67 years (P=0.03) and 68-77 years (P=0.03) though the difference was non-significant when compared with patients <58 years (P=0.06). The KFRE displayed adequate calibration across all age quartiles. The cumulative incidence of kidney failure was overestimated in models that did not account for the competing risk of death and this overestimation was more prominent with older age.

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

TH-OR69

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

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

Methods: Population-level administrative data cohort of 1,109,905 adults (>66 years old) from Ontario, Canada April 1, 2008 and December 31, 2017 with a minimum of 2 eGFR measures (one for baseline > 70 ml/min, one for outcome) were included. Prediction equations stratifying individuals with (n=191,690) and without (n=998,255) ACR were derived, internally validated by bootstrapping and externally validated in 122,148 (22,809 ACR, 99,335 non-ACR) individuals in Manitoba, Canada. The study outcome was a single eGFR measure < 60 ml/min/1.73 m2 with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min and a single eGFR < 45 ml/min as study outcomes.

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

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

TH-OR70

Tubular Secretion of Creatinine and Clinical Outcomes: The AASK Trial

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: This prospective analysis of the African American Study of Kidney Disease (AASK) included 990 participants with baseline measures of iothalamate mGFR, creatinine based eGFR and 24-hour urine CrCl. Tubular secretion of creatinine was calculated in two ways as the difference between 1) CrCl and mGFR (mTScr) and 2) CrCl and eGFR (eTScr). The associations between mTScr and eTScr with incident end-stage kidney disease (ESKD), cardiovascular disease (CVD) and all-cause mortality were evaluated using Cox regression. 

Results: At baseline, the mean mGFR was 45.3 ml/min/1.73 m², and the mean CrCl was 49.3 ml/min/1.73 m². The mean (SD) mTScr and eTScr were 4.0 (14) and 6.5 (14) ml/min/1.73 m². Over a 4.2 years of follow up there were 149 ESKD, 82 all-cause mortality, and 132 incident CVD events. Each 10 ml higher mTScr calculated in two ways as the difference between 1) CrCl and mGFR (mTScr) and 2) CrCl and eGFR (eTScr) significantly increased the risk of ESKD, independent of GFR, proteinuria, or other risk factors. This allows for the incorporation of eTScr into epidemiological studies which many have collected mTScr.

Funding: NIDDK Support

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

Model 1: unadjusted; Model 2: adjusted for age, sex, BMI, race, randomization arm; Model 3: Model 2 + smoking, CVD, systemic BP, hypertension and medications; Model 4: Model 3 + acute proteinuria + baseline eGFR.

FR-OR01

Role of Off-Target Ferrochelatase Inhibition in Vemurafenib Nephrotoxicity

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Background: Complications linked with both cancer and anti-cancer therapeutics can trigger kidney injury. For targeted anti-cancer therapeutics, nephrotoxicity may occur because of on- or off-target mechanisms. In melanoma and other cancers with BRAF kinase activating mutations, targeted small molecule therapeutics such as vemurafenib, and dabrafenib have shown remarkable clinical benefits. However, recent clinical studies have shown that a significant number of patients that receive vemurafenib develop AKI suggesting that polyploidization could be a means to escape cell death. Indeed, we found that polyploid TEC tend to accumulate genome instability and survive, while diploid TEC do not. Of note, virtually all dying cells were cycling based on the FUCCI reporter suggesting that TEC death occurred during the S or G2/M phase. As polyploid TEC increase immediately following AKI, they may be required to survive injury and damage by sustaining renal function. In order to evaluate the functional role of polyploid cells during AKI, we generated YAP1ko mice, where YAP1 is knocked-out specifically in TEC. Indeed, after AKI, YAP1ko mice showed a reduced number of polyploid cells, worsened kidney function and a dramatic reduction of mouse survival, proving that polyploidization is required to survive AKI.

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

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

FR-OR02

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

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

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

Results: After AKI, YAPI is activated driving TEC polyploidization. Polyploid TEC increase in parallel to massive cell death triggered by AKI suggesting that polyploidization could be a means to escape cell death. Indeed, we found that polyploid TEC tend to accumulate genome instability and survive, while diploid TEC do not. Of note, virtually all dying cells were cycling based on the FUCCI reporter suggesting that TEC death occurred during the S or G2/M phase. As polyploid TEC increase immediately following AKI, they may be required to survive injury and damage by sustaining renal function. In order to evaluate the functional role of polyploid cells during AKI, we generated YAP1ko mice, where YAPI is knocked-out specifically in TEC. Indeed, after AKI, YAP1ko mice showed a reduced number of polyploid cells, worsened kidney function and a dramatic reduction of mouse survival, proving that polyploidization is required to survive AKI.

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

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

FR-OR03

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

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

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

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

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

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Proximal Tubule Pannexin 1 Channel Regulates Mitochondrial Function and Cell Death During AKI
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Background: Pannexin 1 (PANX1) channel serves as a conduit for release of small metabolites upon activation during cellular stress and injury. We have previously shown that pharmacological inhibition or genetic deletion of PANX1 in mice prior to injury is protective against renal ischemia-reperfusion injury (IRI). How PANX1 contributes to acute kidney injury (AKI) is unknown. We hypothesized that Panx1 induces cell death by mediating both intracellular and extracellular events.

Methods: We performed or cisplatin-induced AKI in a novel human Panx1 overexpressing mouse (hPANX1-Tg) and in proximal tubule specific Panx1 overexpressing mice (hPANX1-Tgcre) and assessed plasma creatinine, renal expression of neutrophil gelatin associated lipocalin (NGAL), and acute tubular necrosis score. We challenged hPANX1-Tg overexpressing mice with cisplatin and assessed cell death and mitochondrial changes. We next assessed the changes in mitochondria of kidneys from cisplatin challenged hPANX1-Tg animals.

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

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

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

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

Results: GSTM3P1/gstm2-ps1 was markedly induced in the early phase of ischemic AKI but not in the late phase of injury (in vitro and in vivo). HK2 cells, qPCR indicated a significant increase of GSTM3P1 at 3 hours after 1% O2 treatment. In C57Bl/6 mice, gstm2-ps1 was significantly induced in kidneys after 30 minutes of ischemia and 3 hours of reperfusion, which was also accompanied with the suppression of mir-668. In vitro, overexpression of GSTM3P1 led to more renal proximal tubular cell death after ATP depletion. GSTM3P1 overexpression in HEK cells caused significant decrease of the mature form of mir-668. A mir-668 binding site in GSTM3P1 was also confirmed by luciferase assay. We further generated kidney proximal tubule-specific gstm2-ps1 knockout (KO) mouse model. Compared to wild type littermates (WT), the conditional gstm2-ps1 KO mice were significantly protected from renal ischemia-reperfusion injury. Both blood urea nitrogen level [268.18±47.97 mg/dL (WT)] vs 174.42±26.85 mg/dL (KO)] and the serum creatinine level [2.45±0.36 mg/dL (WT)] vs 1.41±0.27 mg/dL (KO)] were remarkably decreased. Consistently, renal tubular damage and apoptosis were significantly suppressed in KO mice, kidney injury score also had lower tubular NGAL.

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

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

Methods: C57Bl/6 wild type (WT) mice underwent bilateral ischemia reperfusion (IR). TIGIT expression and effect on kidney T cell activation and cytokine expression was assessed at baseline and after IR injury by flow cytometry in WT mice. TIGIT knockout (TIGIT KO) mice were used to assess effects on AKI. Human kidney at baseline and post ischemia for nephrectomy had C4D TIGIT measured by flow cytometry.

Results: TIGIT expression increased significantly (p<0.01) on CD4 T cells in proximal tubules compared to controls (15.0±1.5% vs 3.8±0.2%). Furthermore, TIGIT+ CD4 T cells from WT kidneys showed significantly increased expression of activation markers, CD25 (10.9±1.7% vs 2.4±0.2%, p<0.01), CD69 (14.5±1.4% vs 8.8±1.0%, p<0.01) and CD44 (93.9±1.5% vs 74.5±1.7%, p<0.01) compared to TIGIT- CD4 T cells. Intracellular cytokine analysis showed significantly increased IFNγ (50.4±3.3% vs 20.3±3.3%, p<0.01) and TNFα (55.7±5.0% vs 35.4±4.9%, p<0.02) expression by TIGIT+ CD4 T cells compared to TIGIT- CD4 T cells after IR injury in WT mice. TIGIT KO mice had significantly reduced Sgr at 24h (2.1±0.2 vs 2.6±0.1 mg/dL; p=0.03) and 72h (1.3±0.3 vs 2.7±0.4 mg/dL; p=0.02) post IR compared to WT mice. At baseline, renal tubule KOs whose kidneys had significantly (p<0.03) reduced CD4 T cells compared to WT kidneys (59.2±1.7% vs 54.0±0.5%). CD4 T cells from ischemic human kidney had increased TIGIT expression compared to non-ischemic kidney (236.5±127.9 vs 24.75±16.1, p<0.01).

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

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Gastrodin D-Deficient Mice Are Hypersensitive to Necroptosis-Mediated AKI
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Background: Within the last decade, a central role for regulated necrosis (RN) in the pathophysiology of renal ischemia-reperfusion injury (IRI) has been established. RN is an umbrella term for several RN subtypes. With respect to the kidney, necroptosis and ferroptosis are the best studied pathways. However, the role of pyroptosis, a highly inflammatory RN type dependent on the protein GSDMD (gastrodin D), during IRI remain to be defined.

Results: Gastrodin D-Deficient Mice are hypersensitive to necroptosis-mediated AKI. Gastrodin decreases plasma creatinine and inhibits renal expression of neutrophil gelatin associated lipocalin (NGAL) and TNF-α without affecting kidney necrosis.

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

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

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

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

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

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

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

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FR-OR11

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

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Background: Cystine is a product of dietary protein degradation and is considered a pivotal mechanism of kidney protection in response to FMD, SR80/100 and CR. Additionally, dietary preconditioning protocols - fasting mimicking diet (FMD), ketogenic diet (KD), dietary restriction of branched chain amino acids (BCAA), and Caloric restriction (CR) protect from acute kidney injury (AKI) in rodents. Translocation of CR to the clinic is complex. Novel targeted dietary regimes modulating the dietary composition of macro- and micronutrients promise similar protective effects and increased translatability.

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

Results: FMD, SR80/100 and CR efficiently protected from IRI-induced AKI quantified by kidney function, tissue damage and survival rates in mice. Preconditioning with KD yielded moderate benefits after IRI, whereas BCAA failed to protect from renal ischemic damage. Targeted metabolite and proteome profiling revealed overlapping changes in oxidative and hydrogen sulfide (H₂S)-dependent cystine catabolism as a pivotal mechanism of kidney protection in response to FMD, SR80/100 and CR identifying sulfite as its central component. These diet-induced metabolic adaptations were confirmed in humans consuming a low-SAA diet.

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

Funding: Private Foundation Support, Government Support - Non-U.S.
Identifying Diabetic Kidney Disease Signatures in the Nuclei of the Tubular Epithelium Using a Novel Deep Learning Approach

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

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

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

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

Funding: NIDDK Support

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

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Background: Multi-omics techniques could help identify novel therapeutic targets for different types of kidney diseases. CERS6 gene was exclusively enriched in podocytes of normal patients and healthy controls, patient kidney biopsies (n = 44) from an early DKD cohort with the trained CNN.

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

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

Funding: NIDDK Support

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

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

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

Results: Single cell RNA-seq analysis revealed that TGFβ1 treated organoids exhibited a similar fibrotic response to what is observed in human diabetic kidneys. Furthermore, TGFβ1 induced the differentiation of resident stromal cells into activated myofibroblasts, and this was accompanied by the upregulation of fibrogenic genes such as α-smooth muscle actin and transgelin, consistent to what is observed in vivo. Single cell ATAC-seq of iPSC-derived kidney organoids treated with TGFβ1 revealed that TGFβ1 increases chromatin accessibility at all promoters, DNase 1 hypersensitive, and transcription start sites in all cell types present within the organoid. Furthermore, TGFβ1 increased chromatin accessibility at some enhancers and this was cell-type dependent.

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

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

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

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

Results: Each section contained ∼100,000 cells. Single-cell gene expression profile and cell identification by MERFISH allowed us to map the spatial organization of 11 major cell types: PTs, PSCS, EC, DCT, Podo, DTJ, inPT, PC, mTAL, cTAL, and fibroblasts. Podocyte cluster transcripts Cdkn1c, Dendrin, Sema3g, and Epha6 were specifically expressed in glomeruli and Epha6 and Sema3g were significantly increased in diabetes. Top PT5 markers including Ppara, Slc7a7 and Slc5a2 exhibited superficial cortical localization whereas PT1 markers Slc22a19, Acox2 and Kcn3 were in the cortical/medullary region. Myh11 selectively labeled JGA while Nos1 marked the macula densa. Endothelial (EC) markers including Eglf7, Cdh5, Ehd3, Pttn1, Ps16, Ephb4, exhibited distinct anatomic expression, with Ehd3 most highly expressed in glomeruli (figure), while Cd5 and Pvap were low to absent in glomeruli and rather predominated in peri-tubular interstitial.

Conclusions: This application of MERFISH single cell spatial transcriptomics to murine diabetic kidney identified nephron specific cell clusters and confirmed anatomically separate gene expression patterns in PT and EC subpopulations. Funding: Commercial Support - Janssen R&D LLC
mRNA expression in Glomeruli

FR-OR16
Set7 Lysine Methyltransferase Influences Endothelial to Mesenchymal Transition in Experimental Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is the number one cause of renal failure with therapeutic options to prevent its progression limited. In response to hyperglycaemia, the lysine methyltransferase Set7 is known to regulate inflammation and fibrosis, however, its role in DN remains poorly understood. This study defines unique endothelial to mesenchymal transition in experimental diabetic nephropathy.

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

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

Conclusions: These findings support the rationale of targeting Set7 activity as a strategy for developing renoprotective therapies in diabetes. Our studies also show the major cell types regulated by Set7 involved in diabetic injury, we extended studies to human PTC, GEN and podocyte cells.

Funding: Government Support - Non-U.S.

FR-OR17
PTEN-Induced Kinase 1 Exerts a Protective Effect in Diabetic Tubulopathy by Attenuating Necroptosis
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Background: Mitochondria are cell generators that are critical to cell metabolism, survival, and homeostasis. Necroptosis, a programmed form of cell death mimicking features of apoptosis and necrosis, has emerging significance in various human diseases. PTEN-induced serin/threonine kinase 1 (PINK1) is one of the core organizer of mitochondrial quality control and contributes to mitochondrial homeostasis. We designed this study to explore the relationship of PINK1 and tubular cell necroptosis under high glucose conditions and investigate its effects on the progression of diabetic kidney disease.

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

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

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

Funding: Government Support - Non-U.S.

FR-OR18
RTN1A Mediates the Diabetic Kidney Disease Progression Through Endoplasmic Reticulum (ER) Mitochondrial Contacts in Renal Tubular Epithelial Cells
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Background: Renal tubular epithelial cell (RTEC) injury contributes to kidney fibrosis and the progression of diabetic kidney disease (DKD), but the major risk factors contributing to RTEC injury in early DKD remain unclear. We previously showed that the ER-associated E3 ubiquitin ligase RTN1A overexpression increases in RTEC in human and mice with DKD and contributes RTEC injury in vitro and in vivo through activation of ER stress. Here, we will further dissect the role and mechanism of RTN1A in RTEC injury in early DKD.

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

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

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

Funding: NIDDK Support

FR-OR19
Advanced Light Sheet Microscopy and 3D Image Analyses of Kidney Injury, Glomerulosclerosis, and Fibrosis in a Mouse Model of Diabetic Kidney Disease
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Background: Development of novel therapies for diabetic kidney disease (DKD) and other glomerulopathies is challenged by poor translatability of preclinical animal models. Novel transgenic models with 3D light sheet microscopy and advanced image analyses, and advanced image analyses, we aimed to develop a method for quantification of kidney injury and fibrosis in a preclinical mouse model of progressive DKD.

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

Results: In reininAAV UNx db/db mice, tenascin was present in glomeruli as showed by its overlap with podocin. A sub-population of glomeruli with augmented tenascin expression with no overlap of podocin was identified indicating that these glomeruli have global glomerulosclerosis and loss of podocytes. Tubulointerstitial tenascin was limited. These findings correlated with traditional histopathological assessment of glomerulosclerosis scoring and fibrosis quantification in PAS and collagen 3 stained kidney sections, respectively. KIM-1 positive tubuli were also visualized in intact kidneys from reininAAV UNx db/db mice and showed a heterogeneous pattern across the kidney.
KIM-1 was clearly localized to the proximal tubules and was also present in parietal cells in a subpopulation of glomeruli. These observations correlated with 2D IHC stains of KIM-1. Kidneys from healthy controls were KIM-1 negative in both 3D and 2D.

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

**FR-OR20**

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

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

**Methods:** In vitro transcribed IncMGC RNA was mixed with lysates from HK2 cells (human kidney proximal tubular epithelial cells) and immunoprecipitated by MS. IncMGC-interacting proteins were confirmed by RNA immunoprecipitation (RIP) and qPCR. Cas9 and guide RNAs were injected into mouse eggs to create IncMGC-KO mice. Wild type (WT) and IncMGC-KO MMC were treated with TGF-β and RNA expression (by RNA-seq and qPCR) were examined. Results: Several nucleosome remodeling factors including SMARCA5 and SMARCC2 were identified. IncMGC interacts with MS by binding to RIP-qPCR. MMC from IncMGC-KO mice showed no basal or TGF-β-induced expression of IncMGC. Interestingly, several miRNAs in the miR-379 cluster were also reduced in IncMGC-KO MMC compared to WT MMC. Enrichment of histone H3K27 acetylation and H3K4 trimethylation on the IncMGC promoter was increased in TGF-β-treated WT MMC but significantly reduced in IncMGC-KO MMC. ATAC peaks at the IncMGC promoter region as well as many other loci including Col1a2, Col4a3, Col4a4 and CTGF were significantly lower in IncMGC-KO MMC than WT MMC.

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

**Funding:** NIDDK Support

**FR-OR21**

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

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

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

**Results:** The mean number of facilities offering home dialysis in each HRR increased from 15.6 in 2006 to 22.1 in 2016, with for-profit ownership (79.8% in 2006, 87.1% in 2016) and chain affiliation (82.3% in 2006, 91.7% in 2016) increasing over time. While average regional home dialysis utilization rates increased over time, disparities persisted for age, sex, year, and HRR.

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

**Funding:** NIDDK Support

**FR-OR22**

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

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

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

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

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

**Funding:** Other U.S. Government Support

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.**
**Results:** The cohort included 381,623 patients. Over 14% of patients resided in 9-digit ZIP Codes in the highest ADI decile. ADI deciles were linearly associated with adjusted hazards of death and kidney transplantation (table). The highest versus lowest ADI decile was associated with 20% higher rate of death and 72% lower rate of transplantation.

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

**Funding:** NIDDK Support

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**FR-OR24**

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

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

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

**Methods:** This retrospective cohort study includes 47,640 adult in-center HD patients from phases 4-6 of DOPPS (2000-2018) from the US, Japan, Australia, New Zealand, Russia, 7 European and 6 GCC countries. Mean UFR was calculated over one week occurring during the first four-month DOPPS data collection interval. Follow-up for all-cause mortality began after this interval. Risk was estimated using Cox models adjusting for DOPPS phase, country, years on dialysis, age, sex, race, 7 comorbidities, body mass index (BMI), catheter use, 5 labs, Kt/V, residual urine volume, and pre-HD session systolic BP.

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

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

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

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**FR-OR25**

**Outcomes and Predictors Associated with Skin Sodium Concentration in Dialysis Patients**

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

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

**Results:** 52 participants (42 HD, 10 PD) underwent the study procedures. Median follow-up was 423 days (IQR: 290-550). As shown in Figure 1, increasing Skin Na+ quartiles were associated with significantly shorter composite event-free survival (log-rank χ²(4) = 4.73, p < 0.05). Skin Na+ was significantly associated with all-cause mortality (univariate HR 1.059, 95% CI 1.041-1.107; sex-adjusted HR: 1.063, 95% CI 1.046-1.082; age and comorbidity-adjusted HR 1.054, 95% CI 1.017-1.092; sex-adjusted HR: 1.055, 95% CI 1.019-1.093). In multiple regression models, diastolic [Na+], serum albumin and congestive heart failure were significantly associated with Skin Na+ in HD patients (p=0.06).

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

**Funding:** Commercial Support - Vifor Pharma

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**FR-OR26**

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

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

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

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

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

**Funding:** Commercial Support - Vifor Pharma
FR-OR27
Fluid-Related Risk Factors of Peritoneal Dialysis Technique Failure
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Background: Inadequate fluid management in peritoneal dialysis (PD) patients is associated with a higher risk of cardiovascular morbidity and mortality and may result in shortened PD technique survival (Van Biesen et al, 2019). In this analysis, we evaluated the associations between fluid-related clinical factors and PD technique failure within 1 year of treatment initiation.

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

Results: 15,854 automated PD patients (APD; age: 58 years; Kt/Vu: 4.5 mL/min) and 1,547 manual PD patients (CAPD; age: 58 years; Kt/Vu: 4.8 mL/min) were included. 53% of APD patients and 56% of CAPD patients had a PD technique survival ≥ 1 year, and all patients with urine volume ≤ 100 mL, systolic BP > 160 mmHg, history of cardiovascular events and hospitalizations, or weight change ≥ 2 kg between day 1 and day 120 of PD treatment had a higher risk of 1-year PD technique failure (Figure 1).

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

Funding: Commercial Support - Fresenius Medical Care North America

Figure 1: Correlation between change from baseline to Week 12 in WI-NRS and Sleep Quality Questionnaire scores

FR-OR28
Mass Spectrometry-Based Proteomic Analysis of Adsorbed Molecules in a Hexadecyl-Immiscible Cellulose Beads Column for the Treatment of Dialysis-Related Amyloidosis
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Background: Dialysis-related amyloidosis (DRA) is a serious complication in CKD patients undergoing long-term hemodialysis (HD). β2-microglobulin (β2-m)-related amyloid deposition induces osteoarticular disorders including carpal tunnel syndrome. Direct hemoperfusion with a column containing hexadecyl-immiscible cellulose beads (HICB) is used to adsorb circulating β2-m to inhibit the progression of DRA. As use of the column improves joint pain and physical functions; it is possible that the column absorbs not only β2-m but also other molecules associated with amyloidogenesis and inflammation.

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

Results: With high confidence criteria, 200 proteins adsorbed by the HICB were identified (e.g., β2-m SIN, 193.8 ± 143.4; lysozyme SIN, 156.5 ± 47.8). After passing the HICB-containing column, the serum levels of several proteins were decreased as compared with those in the HD dialyzer and HDF hemofilter (e.g., adsorption rate of β2-m, 9.8% vs 38.0 ± 25.0 [P < 0.05]; lysozyme, 79.2 ± 10.9% vs 15.8 ± 18.8% [HD], p < 0.01). In the amyloid deposited in the carpal tunnel, 143 proteins were identified, of which 54 were also found in the HICB-containing column. Cellular matrix metabolic process was one of major Gene Ontology pathways in the common proteins (p = 1.05E-10).

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

Funding: Commercial Support - Kaneka Medix Co

FR-OR29
Effects of NOS3 and Nitric Oxide Releasing Biomatrix Gel on Reducing Intimal Hyperplasia and Vascular Remodeling
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Background: An arteriovenous fistula (AVF) is the preferred type of vascular access in hemodialysis patients. However, nearly 60% of AVFs developed create AVF maturation failure due to venous intimal hyperplasia (IH) formation and poor vascular remodeling (VR). We hypothesize that the endothelial nitric oxide synthase (NOS3) system is critical for reduction of IH and outward VR and local nitric oxide (NO) delivery at the time of VR formation.

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

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

Conclusions: NO3i-NO-cGMP system is a critical regulator of AVF remodeling. Thus NO-releasing gel has great potential to promote clinically successful AVF maturation.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support
**FR-OR31**

**Human PL2R Antibodies Induce Membranous Nephropathy in Minipigs**

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

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

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

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

**Funding:** Government Support - Non-U.S.

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**FR-OR32**

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

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**Background:** Primary membranous nephropathy (MN) is an autoimmune disease caused by autoantibodies against podocyte antigens, leading to glomerular damage, nephrotic syndrome, and potentially end-stage renal disease requiring dialysis or transplant. Phospholipase A2 receptor (PL2R) autoantibodies are found in 70-80% of primary MN patients, co-localize with PL2R and IgG4 glomerular immune deposits, and correlate with disease activity, supporting their causative role in disease pathogenesis. B cell depletion with rituximab is an effective strategy for treatment of primary MN. However, patients often require repeat treatments for disease relapse or maintenance of remission, and infectious serious adverse events are observed in up to 6.2% of rituximab-treated patients, highlighting the need for therapy that induces durable disease remission without generalized immunosuppression. Chimeric antigen receptor T cells have proven clinical ability to induce long-term remission of B cell cancers. We have shown that antigen-based chimeric autoantibody receptor (CAAR) T cells cause DS3-specific B cell depletion in animal models of murine pemphigus vulgaris (mpV) without detectable off-target toxicity, which has led to a phase 1 trial of DS3-CAART in mpV (NCT04422912). This study extends the CAART approach to PL2R MN.

**Methods:** CAARs comprising PL2R immunodominant epitopes linked to CD137-CD28 and CD19 domain SF3 cytokine domains were expressed in primary human T cells and evaluated for specific cytoxicity against anti-PL2R target cells, adsorption of anti-PL2R MN IgG, and potential off-target binding using luciferase assays, ELISA, and commercial membrane proteome arrays.

**Results:** PL2R CAARs directed specific cytolysis of anti-PL2R cell lines targeting major PL2R MN epitopes in the cysteine-rich and C-type lectin 1 and 7 domains. PL2R-CAART cells adsorbed 95-99% of anti-PL2R IgG from MN patient plasma, indicating that PL2R CAARs encompass the major autoantibody-binding epitopes in MN patients. Membrane proteome arrays screened with PL2R CAAR extracellular domains did not identify off-target interactions.

**Conclusions:** CAAR T cells represent a novel strategy for targeted B cell depletion in PL2R MN and may ultimately prove to be valuable for the treatment for a broad range of antibody-mediated diseases.

**Funding:** Commercial Support - Cabala Bio
FR-OR33
New Insights on the Role of C3a/C3aR1 Signaling in Membranous Nephropathy
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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide. MN is characterized by the deposition of anti-podocytoid antibodies within the glomerular subepithelial space. While complement deposition and formation of membrane-attack-complex (MAC) are thought to play a crucial pathogenic role, the exact mechanism of injury in MN is still unclear. We have developed a novel glomerulitis-on-a-chip system (GOAC) using human primary podocytes and glomerular endothelial cells (GEC) to study MN and assess functional response to human MN serum, role of MAC formation and C3a/C3aR1 signaling in MN pathogenesis in addition to in vivo studies.

Methods: GOACs were cultured with serum containing either anti-PLA2R or THSD7A+ MN patients and from healthy individuals (as control). Functional response was assessed by albumin permeability assay. The mechanistic role of MAC and C3a/ C3aR1 signaling pathway was assessed by immunofluorescence, functional analysis, PCR arrays and Western Blotting. Results were further confirmed in GOAC using podocytes1,2,3 and in vivo using THSD7A induced MN in balb/c mice.

Results: Following exposure to sera from MN patients, we have found evidence for human IgG on podocytes and formation of MAC complex, accompanied by albumin leakage. MAC inhibition did not prevent albumin leakage while GOAC supplemented with C3aR1 antagonists as well as GOAC using podocytes4,5,6 were able to prevent glomerular filtration damage and albumin leakage. Efficacy of C3aR1 antagonists in preventing proteinuria was confirmed in mice injected with serum from patients with anti-thrombospondin Ab, substantiating our findings.

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

Funding: NIDDK Support, Private Foundation Support

FR-OR34
C3d-Targeted Factor H Achieves Potent Renal Complement Inhibition and Reduced Glomerular Injury Without Affecting Systemic Complement
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Background: Complement is critical to both the innate and adaptive immune systems, serving an essential role in pathogen response and as an effector of humoral immunity. This system is tightly controlled, and inappropriate activation can cause inflammation and organ injury. Consequently, inhibition has been pursued as a therapeutic strategy for rare complement-driven diseases. However, complement proteins exist in high abundance systemically and undergo rapid turnover, making effective chronic inhibition difficult. In the human system, the rapid turnover of systemic factors means that complement inhibition, systemic blockade raises the risk of infection in patients. As a result, substantial unmet need remains for safer and more effective anti-complement therapies, particularly for chronic diseases.

Methods: We designed a targeted fusion protein to inhibit complement activation in tissue while minimizing systemic blockade. ADX-097 is a humanized anti-C3d monoclonal antibody linked to five N-terminal consensus repeats of the complement inhibitor factor H (H1). We evaluated tissue targeting and both circulating and tissue PK and PD of a mouse ADX-097 surrogate, ADX-118, in Bl6 mice, which exhibit robust glomerular complement activation. We also examined disease-modifying efficacy of ADX-097 in the rat Passive Heymann Nephritis (PHN) model of membranous nephropathy.

Results: We demonstrate that our anti-C3d antibody binds high-density glomerular C3d deposits across a range of renal diseases, indicating that this binding could deliver FH locally. In Bl6 mice, a single subcutaneous dose of 1 mg/kg ADX-118 achieves >75% complement inhibition in glomeruli for at least 7 days post-dose while avoiding systemic complement blockade. A lower, 0.3 mg/kg dose achieves approximately 50% inhibition in glomeruli. In the rat PHN model, a single 1 mg/kg dose of ADX-097 inhibits glomerular complement and significantly reduces urine protein- and albumin-creatinine inhibition in glomeruli. In the rat PHN model, a single 1 mg/kg dose of ADX-097 inhibits >75% complement inhibition in glomeruli for at least 7 days post-dose while avoiding systemic blockade. A lower, 0.3 mg/kg dose achieves approximately 50% inhibition in glomeruli. In the rat PHN model, a single 1 mg/kg dose of ADX-097 inhibits glomerular complement and significantly reduces urine protein- and albumin-creatinine inhibition in glomeruli.

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

Funding: NIDDK Support, Private Foundation Support

FR-OR35
Differentiating Steroid-Sensitive Minimal Change Disease and Primary and Secondary Focal Segmental Glomerulosclerosis: A Proteomics-Based Approach
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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are common causes of nephrotic syndrome. Whether distinct molecular mechanisms are involved in the pathogenesis of MCD and FSGS remains unclear. We used proteomic studies in human kidney biopsies to characterize the differentiating molecular phenotype of steroid-sensitive MCD and primary and secondary FSGS.

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

Results: 733 and 701 significant differentially expressed proteins were detected between MCD, and pFSGS and sFSGS respectively. Proteins regulating cell-cell and cell-matrix adhesion and differentiation (THY1, TRIP6, ACTN3, ACTN1, ITGA7, ITGB2, COL6A1, MMP9, FN1) were significantly upregulated in glomeruli of pFSGS compared to MCD. In the glomeruli of sFSGS, immune regulatory pathways predominantly from the complement (C3, C5, C6, C8A, C8B, C9, CFHR1, CFHR5, CFH) were upregulated compared to MCD (Figure 1). FN1, EF2/4AK, MAP2K3, PHKB, INTS12, BET1 were the most significantly overexpressed proteins in pFSGS compared to MCD.

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

Funding: Clinical Revenue Support

FR-OR36
Association of HLA-DPB1*04:01 and Maintenance of Remission in ANCA-Associated Vasculitis
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Background: Genome wide association studies identified HLA-DPB1*04:01 in ANCA vasculitis and observational studies suggest a biological role. We explored the interaction between HLA/PR3 peptide and association with clinical disease remission.

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

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

Conclusions: Affinity between PR3*04:01* and HLA-DPB1*04:01 is reduced among patients in long-term clinical disease remission. These data suggest that the interaction is dynamic and that it could determine the subsequent immune response of T cell activation and maintenance of immunological remission. When HLA-DPB1*04:01 does not present PR3*04:01 as an antigen, it is recognized by autoreactive T cells. The peptide-HLA interaction may be the link explaining why patients with PR3-ANCA and HLA- DPB1*04:01 are unable to maintain disease remission.

Funding: NIDDK Support
FR-OR37
Leukotriene B4-BLT1 Axis Controls Neutrophil Accumulation via Fcγ Receptor-Dependent Leukotriene B4 Production in Experimental Glomerulonephritis
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Background: Eicosanoids are biologically active lipid mediators generated rapidly at sites of inflammation. Leukotrienes are one of the eicosanoids generated through the metabolism of arachidonic acid by 5-lipoxygenase and 5,6-lypoxigenase. Although it is generally known that leukotriene B4 (LTB4) functions as a potent chemotactic factor for neutrophils via its receptor BLT1, the role of LTB4 and BLT1 axis on glomerulonephritis has not been clarified.

Methods: We used the nephrotoxic serum nephritis model, which mimics human glomerulonephritis. To investigate the effect of LTB4-BLT1 axis on glomerulonephritis, we used BLT1-knockout (KO) mice. Specifically, serological and histological analyses were performed in acute and chronic phases. We used LC/MS/MS to measure LTB4 in the kidney. To confirm LTB4 production by neutrophils, we activated the Fcγ receptor of neutrophils by cross-linking with IgG.

Results: On day 7 after onset of nephritis, wild-type (WT) mice showed severe proteinuria, crescent formation accompanied by macrophage infiltration, which was markedly attenuated in BLT1-KO mice. Next, we examined neutrophil infiltration in glomeruli in acute phase; the number of neutrophils in glomeruli peaked at 6 hours after onset both in WT and BLT1-KO mice, but was markedly lower in BLT1-KO mice. Complement activity and chemokines were comparable in both groups. Then, we measured LTB4 in the kidney and found that LTB4 production occurred within an hour of onset, indicating a dominant effect of the LTB4-BLT1 axis on early neutrophil infiltration. In vitro studies demonstrated that WT, production was dependent on activation of Fc receptors. On day 1 after onset, BLT1-KO mice exhibited reduced proteinuria and attenuated endothelial damage. Furthermore, administration of BLT1 receptor antagonists after onset relieved nephritis, strongly indicating its therapeutic effect. Finally, BLT1-positive cells infiltrated glomeruli of patients with ANCA-associated vasculitis, suggesting that the LTB4-BLT1 axis might play important roles in human glomerulonephritis.

Conclusions: Our results revealed that blockade of initial neutrophil infiltration by inhibition of the LTB4-BLT1 axis mitigated nephritis and could counteract subsequent macrophage infiltration. The LTB4-BLT1 might be a promising therapeutic target for glomerulonephritis.

FR-OR38
mTOR Activity of Macula Densa (MD) Cells Is a Major Determinant of Glomerular Structure and Function
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Background: Macula densa (MD) cells are paracrine regulators of renal hemodynamics and renin and were recently reported to feature a high rate of protein synthesis. Since the central regulator of protein synthesis is the mTOR pathway, the purpose of the present study was to examine if the MD mTOR signaling in the maintenance of glomerular structure and function.

Methods: Inducible MD-specific mTOR gain-of-function (MD-mTOR)1 mice were generated by crossing nNOS/CreERT2-mTmG and TSC2/fl mice. Protein synthesis activity in vivo at the single-cell level was quantified using O-propargyl-puromycin (OPP) fluorescence imaging and histological analysis in Sox2-tdTomato and MD-GFP mice. Glomerular filtration rate (GFR) was measured via transradial detection of FITC-sinistrin plasma decay (MediBeacon) and renal blood flow (RBF) was quantified by intravital microscopy.

Results: Sox2-tdTomato mice and the OPP assay showed the highest protein expression in the MD among all renal cell types. Immunolabeling validated MD-specific TSC2 KO and upregulated pS6K in MD-mTOR+ mice. MD-mTOR+ significantly increased the overall rate of protein synthesis in MD cells (1.300±0.057) vs control (0.944±0.039). Physiological activation of MD cells by low salt diet further enhanced MD protein synthesis in both WT (1.36±0.035) and MD-mTOR+ (1.48±0.056) mice, which was blocked by Rapamycin treatment. MD-enriched proteins such as CCN1, CCN3, PappA, and CxCl4 had significantly higher expression in response to MD-mTOR+ GFR was significantly elevated in MD-mTOR+ mice compared to WT (1981±121.30 vs 1444±99.48 µL/min/100 g BW) with similar changes observed with respect to RBF based on single afferent (AA) efferent arteriole (EA) blood flow, vessel diameter and glomerular area measurements. COX2, mPGES1, renin, the length of basal MD cell processes (maculae copulatrix) and MD cell number/plaque were also significantly increased in MD-mTOR+ vs WT mice.

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

Funding: NIDDK Support

FR-OR40
Intravital Imaging Reveals Glomerular Capillary Enlargement and Endothelial/Immune Cell Activation Early in Alport Syndrome
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Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in type IV collagen that lead to defective glomerular basement membrane, damage of the glomerular filtration barrier (GFB), and progressive kidney disease. While the genetics of AS is well known, the molecular and cellular mechanisms of disease pathogenesis have been elusive, hindering the development of effective, specific, and mechanism-based therapies. Here we aimed to obtain direct visual clues on the major drivers of AS progression by performing high-power intravital multiphoton microscopy (MPM) of the local kidney tissue microenvironment in a mouse model of AS, with translation to the human condition.

Methods: In vivo kidney MPM imaging of transgenic Alport mice (Col4a5 mutant) aged 2 and 5 months of age was coupled with renal ischemia and histology. Endothelial glyocalyx was labeled with FITC-WGA, T cells with anti-CD3-Alexa594, and with anti-CD8-Alexa647 antibodies, and plasma with Albumin-Alexa680. Animals received hyalurondise (30U iv). AS patient renal biopsy specimens with minimal change disease controls were used for semiquantitative fluorescence histological analysis and single glomerular spatial proteomics (Nanostring).

Results: Severely distended glomerular capillaries and aneurysms were found in AS mice accompanied by numerous microthrombi, increased glomerular endothelial glyocalyx, increased immune cell and albumin leakage throughout the glomerulus and interstitial fibrosis by 5 months of age with an intermediate phenotype at 2 months. Histological and single glomerular spatial proteomics analysis of AS patient biopsies confirmed the presence of dilated glomerular capillaries, activated T cells, endothelial
FR-OR41

Comparative Human and Mouse Kidney Transcriptionites Identify ELF4 as Potential Therapeutic Target
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Background: Mouse models provide an excellent tool to study kidney disease pathogenesis, but little is known how well mouse models recapitulate molecular changes of human CKD.

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

Results: Using comparative bioinformatics approaches we identified 1256 genes and 47 transcription factors that were commonly regulated in all mouse CKD and in patients with CKD. In particular we identified ELF4 and ELF4 transcription factors as they were elevated in both all mouse models and patient samples. mice with genetic deletion of elf4 was healthy at baseline and showed protection from FA and cisplatin induced kidney fibrosis and disease. We found that ELF4 is mostly expressed in immune cells and influenced inflammation. Therapeutic inhibition of ELF4 was tested by injection of siRNA, which showed similar protection of kidney disease.

Conclusions: Comparative transcriptionites identified EIF4 as one of the key conserved transcription factor in human and mouse CKD. Genetic deletion or pharmacological inhibition of EIF4 protected mice from fibrosis.

FR-OR42

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

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

Results: We identified 62 proteins which were associated with eGFRcr and 42 with eGFRcc (p=0.05/1,318). Of these, 19 were associated with both kidney function measures in a directionally consistent manner, nominating novel gene annotations in 18 of the 19 genetically associated regions. The enzyme isopentenyl-diphosphate delta isomerase 2 (DDI) showed the strongest associations (p=4.3e-37, p=1.0e-15). Two novel transcripts for eGFRcr and eGFRcc, respectively (p=0.05/235,763). Of these, 544 were associated with both kidney function measures, including 13 of the 19 PWAS genes. There were also 27 identified in kidney tubule expression, including DACH1 and MANB4, which were recently identified as contributors to kidney fibrosis.

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

Funding: Government Support - Non-U.S.
Conclusions: We suggest the expression of WT1 mRNA as a surrogate for quantifying podocytes. We propose the decrease of TRPC6 and GRM1 mRNA in urinary podocytes as a marker helpful to provide complementary information to Bx. These genes are useful for monitoring actin cytoskeleton remodeling in podocytes that contributes to glomerular damage in course of renal disease.

**FR-OR45**

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

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

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

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

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

**Funding:** Government Support - Non-U.S.

**FR-OR46**

Soluble Fhl1 Binds to Anti-Inflammatory Macrophones in the Kidney

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**Background:** Soluble Fhl1 (sFhl1), a decoy receptor of VEGF ligands, is a key regulator of angiogenesis. High systemic levels of sFhl1 have been linked to the pathogenesis of preeclampsia. However, we have previously reported that treatment with low concentrations of sFhl1 ameliorates kidney damage and inflammation. Specifically, sFhl1 targets macrophones, suggesting that sFhl1 has nephroprotective immunomodulating effects. Here, we studied the presence of sFhl1 in human kidney diseases and investigated the expression and direct binding of sFhl1 to macrophones.

**Methods:** Renal biopsies of patients with various kidney diseases (IgA, LN, DN, FSGS, MCD) and pre-transplant control biopsies were stained for sFhl1, CD163 and CD68. Cultured macrophones were incubated with increasing concentrations of sFhl1. H1s, after which membrane binding was measured using flow cytometry. For this, THP-1 monocytes were differentiated with PMA and activated with IFN-γ and LPS or IL-4, primary macrophages were differentiated using GM-CSF or M-CSF.

**Results:** A patchy pattern of sFhl1 staining colocalizes with CD163/CD68-positive cells in tubulointerstitial areas and with CD68-positive cells in glomeruli. No quantitative differences in renal sFhl1 levels were observed in patients with kidney disease and controls. Flow cytometric analysis revealed that sFhl1 binds to PMA-differentiated THP-1 macrophages but does not bind to THP-1 monocytes. Activation with IFN-γ and LPS upregulates sFhl1 binding to THP-1 macrophages. However, IL-4 activation of THP-1 macrophages strongly increases membrane sFhl1 binding. Furthermore, IL-4 activation upregulates sFhl1 mRNA expression in THP-1 macrophages. In primary macrophages, sFhl1 binding was higher in macrophages differentiated with GM-CSF compared to M-CSF.

**Conclusions:** Our results suggest that sFhl1, while typically associated with angiogenesis, binds to anti-inflammatory macrophages in the human kidney. Alternative activation of macrophages by IL-4 strongly induces sFhl1 production and increases direct binding of sFhl1 to the cell surface membrane. We infer that sFhl1 functions as an autocrine stimulus of anti-inflammatory macrophages, independent of its antiangiogenic properties. Since anti-inflammatory macrophages mediate repair after kidney injury, our work suggests the potential of sFhl1 as a therapeutic tool.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-OR48

Complementary Quantification of Interstitial Fibrosis and Tubular Atrophy (IFTA) for CKD Cases of the Kidney Precision Medicine Project
Brendon Lutnick,1 Avi Z. Rosenberg,1 Laura Barisoni,2 Charles E. Alpers,3 Yijiang Chen,4 Andrew Janowczyk,5 Anant Madabhushi,1 Jose Torrealba,1 Astrid Weiss6,7 Isaac E. Stillman,1 Leal C. Herlitzi,8 Luis Rodrigues,2 Jonathan E. Zuckerman,8 Sanjay Jain,9 Ulysses G. Balis,1 Kuang-Yu Jen,10 Pinaki Sarid.1 Kidney Precision Medicine Project 1University of Buffalo, Buffalo, NY; 2Duke University, Durham, NC; 3University of California Los Angeles, CA; 4Washington University in St Louis, St Louis, MO; 5University of California Davis, Davis, CA; 6University of Michigan, Ann Arbor, MI, 7Universidade de Coimbra, Coimbra, Portugal; 8The University of Texas Southwestern Medical Center, Dallas, TX, 9Washington University, St Louis, MO; 10University of Utah Health, Salt Lake City, UT.

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

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

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

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

Funding: NIDDK Support

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

FR-OR49

Complement Convertases in Glomerulonephritis: An Explainable Artificial Intelligence-Assisted Renal Biopsy Study
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Background: Complement activation is crucial in the pathogenesis of C3 glomerulopathy (C3GP). It is likely also involved in other forms of glomerulonephritis (GN), however, here, intensity, significance, and predominant activation pathways are less clear.

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

Results: In C3GP and PIGN a clear predominance of the alternative convertase (mean 8410 and 14493 signals/sqmm) whereas IC-MPGN (mean 798 signals/sqmm) and MN (mean 278 signals/sqmm) were not significantly different from the control group (mean 176 signals/sqmm). Interestingly, cases with IgAN revealed increased densities for the alternative convertase (mean 2088 signals/sqmm) but only very similar increased densities for the classical/lectin convertase (225 signals/sqmm).

Conclusions: This work shows the applicability of human-machine collaboration based on xAI to characterize and quantify local complement activity. The results reveal insights into the role of complement in the pathogenesis of different forms of glomerulonephritis. Moreover, this opens the possibility to assess local activities of the alternative and the classical/lectin pathway C3/C5 convertases in individual patients.

FR-OR50

Cubulin Is a Novel Target Antigen in Anti-Brush Border Disease
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Background: Anti-brush border antibody disease (ABBA) is an autoimmune kidney disease that frequently progresses to kidney failure. It is characterized by proximal tubule damage, IgG-positive immune deposits along the tubular basement membrane (TBM), and circulating autoantibodies directed against the brush border. To date, the multifilament receptor megalin (also known as LDL receptor-related protein 2, LR2P) is the only target antigen associated with ABBA.

Methods: Here, we investigated a patient with LR2P-negative ABBA and applied mass spectrometry and confocal microscopy to identify a novel target antigen.

Results: A 75-year-old European female patient with past history of hypertension, type 2 diabetes and stage G3/A1 CKD was referred for rapid decline in kidney function (decrease in CKD-EPI estimated glomerular filtration rate from 37 to 16 mL/min per 1.73 m2 over a few months). This was associated with new onset proximal tubule dysfunction, as attested by low molecular weight proteinuria and aminoaciduria. There was no evidence of monoclonal gammapathy, systemic autoimmune disease or exposure to environmental toxins, and serum cobalamin level was normal. The kidney biopsy revealed a protracted pattern of tubular injury, granular IgG deposits along the TBM, with a predominance of IgG subclass, and electron-dense deposits in the TBM on ultrastructural analysis. There was no light chain restriction. Although indirect immunofluorescence showed reactivity of the patient’s serum against normal kidney brush border, consistent with the diagnosis of ABBA, immunofluorescence failed to detect LR2P within TBM deposits. Protein G immunoprecipitation followed by mass spectrometry revealed cubulin (CUBN), another member of the endocytic/megacortin protein superfamily, that was not previously present within immune complexes eluted from frozen biopsy tissue. Confocal microscopy confirmed CUBN specifically colocalized with IgG in the TBM. Such colocalization was specific to the disease and not observed in other immune complex-mediated tubulointerstitial diseases, including LR2P nephropathy, IgG4-related kidney disease, idiopathic hypocomplementemic interstitial nephritis, lupus nephritis, or polymavirus nephritis.

Conclusions: CUBN is a novel target antigen in ABBA.

Funding: Government Support - Non-U.S.

FR-OR51

The Effect of Dapagliflozin on Rate of Kidney Function Decline in Patients with CKD: A Prespecified Analysis from the DAPA-CKD Trial
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Background: Dapagliflozin reduced the risk of kidney failure in patients with chronic kidney disease (CKD) with and without type 2 diabetes in the DAPA-CKD trial (NCT03036150). This pre-specified analysis assessed the effect of dapagliflozin on the rate of change in estimated glomerular filtration rate (eGFR) slope.

Methods: DAPA-CKD trial patients with urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g and eGFR 25–75 mL/min/1.73 m2 were randomized to dapagliflozin 10 mg or placebo once daily, added to standard care. We analysed eGFR slope using
mixed effect models with different slopes from baseline to Week 2 (acute change); Week 2 to end-of-treatment (chronic eGFR slope); and baseline to end-of-treatment at median 2.3 years (total eGFR slope).

Results: In the overall cohort, dapagliflozin compared to placebo slowed mean eGFR decline from baseline to end-of-treatment by 0.9 mL/min/1.73m²/year (95% CI 0.6–1.3). Dapagliflozin compared to placebo caused an acute eGFR decline of 2.6 mL/min/1.73m² (95% CI 2.3–3.1) and 2.0 mL/min/1.73m² (95% CI 1.4–2.7), in patients with and without type 2 diabetes, respectively. Thereafter, dapagliflozin compared to placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (chronic eGFR slope mean difference 2.3 mL/min/1.73m²/year (95% CI 1.9–2.6)) than in those without type 2 diabetes (1.3 mL/min/1.73m²/year (95% CI 0.7–1.8)); interaction p=0.005. The effect of dapagliflozin compared to placebo on total slope in patients with and without type 2 diabetes was 1.2 mL/min/1.73m²/year (95% CI 0.8–1.6) and 0.5 mL/min/1.73m²/year (95% CI -0.1–1.0); interaction p=0.04, respectively. The total eGFR slope was steeper in patients with higher baseline HbA1c and UACR; the beneficial effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA1c and UACR.

Conclusions: Dapagliflozin significantly slowed long-term eGFR decline in patients with CKD. The mean difference in eGFR slope between dapagliflozin- and placebo-treated patients was greater in patients with type 2 diabetes, with higher baseline HbA1c with CKD. The mean difference in eGFR slope between dapagliflozin- and placebo-treated patients was greater in patients with type 2 diabetes, with higher baseline HbA1c and UACR. The total eGFR slope was steeper in patients with higher baseline HbA1c and UACR; the beneficial effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA1c and UACR.

Funding: Commercial Support - AstraZeneca

FR-OR53
Effects of Daprodustat on Hemoglobin and Quality of Life in Patients with CKD: Results of the ASCEND-NHQ Randomized, Double-Blind, Placebo-Controlled Trial
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Background: Daprodustat (dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being developed for treating anemia of chronic kidney disease (CKD). In a Phase 3 trial in non-dialysis dependent (ND) CKD patients, we evaluated the effect of dapro vs placebo (PBO) on hemoglobin (Hb) and the SF-36 quality of life Vitality score (fatigue) over 28 weeks.

Methods: Adults with CKD stage 3–5, Hb 8.5–10.0 g/dL, transferrin saturation ≥15%, ferritin 450 mg/mL without recent rEPO use were randomized 1:1 to dapro or PBO to maintain Hb 11.0–12.0 g/dL (NCT03409107). Primary endpoint was mean change in Hb between baseline (BL) and the evaluation period (mean over Wk 24–28). Principal secondary endpoints were 1) proportion with ≥1 g/dL increase in Hb, 2) mean change in SF-36 Vitality score (fatigue) between BL and Wk 28. SF-36 Vitality responder (≥40% increase in blood pressure (BP) elevations were secondary endpoints. Superiority for all endpoints was tested (1-sided α=0.025).

Results: 614 ND-CKD patients were randomized. BL demographic characteristics were balanced; Hb was similar (9.73 g/dL dapro, 9.71 g/dL PBO). The adjusted mean difference (AMD) in change in Hb was 1.40 g/dL (95% CI 1.23, 1.56; P<0.001). A greater proportion on dapro had a ≥1 g/dL increase in Hb from BL (77% vs 18%; P<0.001). Adjusted mean (SE) SF-36 Vitality score increased by 7.3 (1.1) points (dapro vs 1.9 (1.2) points (PBO); AMD at Wk 28 was 5.4 (95% CI 2.2, 8.6; P<0.001; Figure). 58% on dapro vs 40% on PBO were SF-36 Vitality responders (difference 18%; 95% CI 14%, 22%). While more BP elevations occurred in dapro vs PBO (32% vs 26%, p=0.07), dapro’s overall effect on BP was similar to PBO. Rates of adverse events were similar (dapro 69% vs PBO 71%).

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

Funding: Commercial Support - GlaxoSmithKline

FR-OR52
Phenome-Wide Association Study of Common Genetic Variants in SGLT2 and Health Disparities in Kidney Outcomes
Mona Mashalvand,1,2 Cassianne Robinson-Cohen,1,2,1 Hua-Chang Chen,1,2 Elvis A. Adewuyi,3 Ran Tao,1,2 Zhizhong Yu,1,2 Lee Wheless,1,2 Cecilia P. Chung,1,2 Adriana Hung,1,2 1Vanderbilt University, Nashville, TN; 2Vanderbilt Nashville VA, Nashville, TN.

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

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

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

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

Funding: Veterans Affairs Support

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

FR-OR54
Integrated Efficacy and Safety of Bardoxolone Methyl in CKD
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Background: Bardoxolone methyl (Bard), an Nrf2 activator, has been studied in multiple CKD trials. To further characterize the safety and efficacy of Bard, we performed integrated analyses across all studies conducted with Bard in CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR5

Renal Outcomes Associated with Direct Acting Anticoagulant Therapy in Patients with Hepatitis C Virus Infection
Fredriq Thomas,1 Praveen Kumar Potukuchi,1 Ankur A. Dashputre,2 Keichi Sumida,3 Miklos Z. Molnar,4 Elani Strej,3 Kamyar Kalantar-Zadeh,2 Csaba P. Kovesdi,2 1The University of Tennessee Health Science Center, Memphis, TN; 2University of Utah Health, Salt Lake City UT; 3University of California Irvine, Irvine, CA; 4VA Memphis Medical Center, Memphis, TN.

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

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

Results: We identified 114,358 patients with HCV infection, of whom 58,045 (51%) received a course of DAA therapy between 2013-2018. The overall mean (SD) age at HCV diagnosis was 55.0 (7.5) years, 97% were male, 38% were African American, the mean (SD) eGFR was 92 (17) mL/min/1.73 m2 and 8% had proteinuria. There were 497 ESKD events and 26,684 composite events over a median follow-up of 11.5 years. DAA therapy was associated with lower risk of ESKD and the composite event (multivariable adjusted HRs and 95%CI: 0.43, 0.31-0.61 and 0.62, 0.60-0.63) [table].

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

Funding: Veterans Affairs Support

FR-OR56

The Comparative Effectiveness and Safety of Direct Oral Anticoagulants (DOAC) and Warfarin Initiation in Adults with Atrial Fibrillation (AF) by eGFR Category
Min Joon Martin P. Gallagher. KODIAc-AF Project Team The George Institute for Global Health, Newtown, New South, Australia.

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

Methods: We conducted an international multicenter cohort study (2011-2018) using healthcare data from 5 jurisdictions across Australia (666 participants of the 45 and Up Study [among 267153 recruited in 2006-09] with data linked to hospital/laboratory data [by eGFR] and the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data provided by Services Australia; all linked data accessed via SURE) and Canada (73876 patients in AB,BC,MB,ON; record linkage of provincial administrative/laboratory data). We propensity score matched adults with a new dispensation of a DOAC (rivaroxaban, apixaban, dabigatran) or warfarin, who had AF and a recorded eGFR grouped as <60, 60-59.30-44, <30mL/min/1.73m2. Chronic dialysis or kidney transplant recipients were excluded. We assessed 2 composite outcomes within 1 year of initiating either therapy: ischemic (all-cause death, ischemic stroke or TIA) and bleeding (intracranial, gastrointestinal or other). We used Cox regression to estimate the hazard ratios (HRs[95%CI]) of outcomes across eGFR categories and summarized centre data in random effects meta-analysis.

Results: A total of 74542 eligible patients were included, among whom there were 6923(9.2%) ischemic and 1572(2.1%) bleeding events recorded. Across eGFR groups, DOAC initiation was associated with lower or similar risk for the ischemic outcome compared with warfarin initiation (pooled HR[95%CI] for eGFR groups: 0.74[0.69-0.79], 0.76[0.54-1.07], 0.68[0.61-0.75] and 0.86[0.76-0.98], respectively). Similar results were observed for bleeding (0.75[0.65-0.86], 0.81[0.65-1.01], 0.82 [0.66-1.02], 0.71[0.52-0.99], respectively). There was no evidence of heterogeneity across jurisdictions except for eGFR 45-59mL/min/1.73m2 for the ischemic outcome (p=.77).

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

Funding: Government Support - Non-U.S.

FR-OR57

Adiposity and Obesity-Related Metabolomics: The CRIC Study
Zihe Zheng,1 Harold I. Feldman,1 Amanda H. Anderson,2 Eugene P. Rhee,3 Casey Rebholz,4 Wei Yang,1 Sushrut S. Waikar,7 Jesse Y. Hsu,8 Rupal Mehta,6 Sylvia E. Rosas,2 Ana C. Ricardo,8 Chi-yan Hsu,7 Jing Chen,2 Vasan S. Ramachandran,2 Robert G. Nelson,3 CRIC Biomarkers Consortium; CRIC Study ‘University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ’Tuane University, New Orleans, LA; ’Massachusetts General Hospital, Boston, MA; ’Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; ’Boston University, Boston, MA; ’Northwestern University Feinberg School of Medicine, Chicago, IL; ’Joslin Diabetes Center, Boston, MA; ’University of Illinois at Chicago, Chicago, IL; ’University of California San Francisco, San Francisco, CA; ’National Institutes of Health, Bethesda, MD.

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

Methods: Among 1,529 CRIC participants with metabolomics data (Broad Institute) we applied consensus clustering with K-means on 20 adiposity-obesity and comorbidity risk, high obesity risk, and high diabetes risk) associated with CKD progression. 79 metabolites on the associations of patient subgroups with CKD progression using Aalen additive hazards models. For those statistically significant mediators, we estimated the HRs of CKD progression for each 2-fold increment in metabolite level using Cox model.

Results: We discovered 3 AOR CKD subgroups (with low obesity/diabetes risk, high obesity risk, and high diabetes risk) associated with CKD progression. 79 metabolites were significant mediators (p<0.05) for this subgroup-outcome association. After Bonferroni correction (p<0.63×10−10) and adjusting for eGFR, 11 metabolites were associated with a lower hazard and 9 with an increased hazard of CKD progression (Table). After additional adjustment for covariates, 4 metabolites remained statistically significantly associated with CKD progression.

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

Funding: NIDDK Support

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Underline represents presenting author.
Findings from Landmark Trials, Other Kidney Trials, and Observational Studies

Table: The associations of individual mediator metabolites with CKD progression: using Cox proportional hazard models

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Adjusted for eGFR</th>
<th>Fully adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Creatine</td>
<td>2.20 (1.78-2.72)</td>
<td>2.20 (1.78-2.72)</td>
</tr>
<tr>
<td>Urea</td>
<td>2.10 (1.63-2.73)</td>
<td>2.10 (1.63-2.73)</td>
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<tr>
<td>Citrate</td>
<td>1.70 (1.26-2.30)</td>
<td>1.70 (1.26-2.30)</td>
</tr>
<tr>
<td>Glutamine</td>
<td>1.30 (0.99-1.72)</td>
<td>1.30 (0.99-1.72)</td>
</tr>
</tbody>
</table>

a Adjusted for age, gender, race/ethnicity, smoking status, asthma, diabetes, BMI, and CKD severity.

Results: We identified three independent genome-wide significant nucleotide polymorphisms (SNPs), rs4917 (p=1.7 x 10^-10), rs2077119 (p=3.3 x 10^-10), and rs2077073 (p=3.1 x 10^-10) in the AHSG gene encoding fetuin-A. The three SNPs together explained 18.3% of the variation in serum T50. Quantitative trait locus analysis revealed that all three SNPs have effects detectable at blood protein level of fetuin-A. Associations with outcomes were studied in 8,556 patients using the community-based Rotterdam study (RS) to examine the association between the genetic variants and all-cause mortality in the general population and in a subgroup of CKD patients. After adjustment for multiple factors, including age, sex, hypertension, BMI, diabetes, and CKD severity, we identified four bacteria that were associated with eGFR at an FDR < 0.05. Additional adjustment for kidney disease options was assessed at both visits.

FR-OR58

Association Between the Gut Microbiota and Kidney Function
Christoph Nowak,1 Johan Amlov,2 GUTSY Research Consortium \( ^{1} \) Karolinska Institutet, Stockholm, Sweden; \( ^{2} \) Högskolan Dalarna, Falun, Sweden.

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

Methods: We studied the composition and predicted function of the gut microbiota based on shotgun whole-genome sequencing of microbial DNA in fecal samples collected from 9,784 adults enrolled in the longitudinal, population-based Swedish SCAPIS cohort study. Linear regression adjusted for technical variables, age, sex, Shannon diversity index and (in sensitivity analysis) established kidney disease risk factors was used to identify associations between the log(x+1)-transformed relative frequencies of metagenomic species and estimated glomerular filtration rate (eGFR). Additional sensitivity analyses included stratified analyses for gender, hypertension and diabetes mellitus. The Benjamini-Hochberg false discovery rate (FDR) multiplicity correction was used.

Results: We included 5,130 women (57.5 ± 4.3 years) and 4,658 men (57.6 ± 4.2 kg/m²), of whom 833 had CKD (age 75.5 ± 9.9 y, 57% female, 63% hypertension, BMI 27.3 ± 4.9 kg/m²), from whom we used the community-based Rotterdam study (RS) to examine the association between the genetic variants and all-cause mortality in the general population and in a subgroup of CKD patients. After adjustment for multiple factors, including age, sex, hypertension, BMI, diabetes, and CKD severity, we identified four bacteria that were associated with eGFR at an FDR < 0.05. Additional adjustment for kidney disease options was assessed at both visits.

FR-OR59

Genetic Determinants of Serum Calcification Propensity and Mortality Risk in CKD
Amber de Haan,1 Fariba Ahmadzadeh,2 Peter J. Van der Most,3 Zohra Kamali,4 Alireza Ani,5,6 Stephan J. Bakker,2 Harlod Snieder,5 Maryam Kuramitsu,4 Andreas Pasch,5 Mark Eggelsheim,5 Martin H. De Borst,7 Universiteit Medisch Centrum, Groningen, Netherlands; 2Erasmus MC, Rotterdam, Netherlands; 3Johannes Keurker Universiteit Lijn, Linz, Austria; 4Calcis AG, Bern, Switzerland; 5Rijksuniversiteit Groningen, Groningen, Netherlands.

Background: Serum calciprotein particle maturation time (T50), a measure of calcification propensity, is associated with cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). Here, we aimed to identify genetic loci for serum T50 and examine whether these loci are linked with adverse outcomes.

Methods: We performed a genome-wide association study (GWAS) of serum T50 in 2,739 community-dwelling individuals of mostly European descent. Subsequently, we used the community-based Rotterdam study (RS) to examine the association between the identified variants and all-cause mortality in the general population and in a subgroup of CKD patients, applying multivariate logistic regression analysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

FR-OR60

Decision Aid for Renal Therapy (DART) Reduces Decision Conflict and Improves Knowledge Among Older Adults with Advanced CKD: A Randomized Clinical Trial
Daniel E. Weiner,1 Dena E. Rikfin,2 Elisa J. Gordon,3 Ana P. Rossi,4 Hocine Tighiouart,1 Sarah Levine,1 Jack Degnan,3 Brianna R. Kurumitsu,4 Lexi Sewall,7 Tamara Isakova,3 Susan Koch-Weser,1 Keren Ladin,1 DART Research Team \( ^{1} \) Tufts Medical Center, Boston, MA; \( ^{2} \) University of California San Diego, La Jolla, CA; \( ^{3} \) Piedmont Healthcare Inc, Atlanta, GA; \( ^{4} \) Northwestern University, Evanston, IL; \( ^{5} \) Tufts University School of Medicine, Boston, MA; \( ^{6} \) Tufts University, Medford, MA; \( ^{7} \) Maine Medical Center, Portland, ME.

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

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

Results: Among 363 participants, 180 were randomized to education and 183 to DART; 162 (89%) completed DART. Mean age was 78 years, mean eGFR was 23 ml/min/1.73 m², 78% were white and 48% had diabetes. Groups were balanced at baseline. At first follow-up, DCS score improved significantly more among the DART group [mean difference (95% CI)=-8.7 (5.2, 22.3)]. Participants who randomized to DART (n=100) compared to usual education (n=100) had a 3.2% (0.5, 5.9) decrease in DCS score. DART was also associated with a 7.2% (3.7, 10.7) greater improvement in knowledge.

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

Funding: Private Foundation Support

Decisional Conflict by Randomization Group

SA-OR01

Identification of a Special Cell Type as a Determinant of the Kidney Tropism of SARS-CoV-2
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Background: Coronavirus disease-2019 (COVID-19) is an infectious disease caused by a novel discovered coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The kidney tropism of SARS-CoV-2 has been well-validated clinically and often leads to various forms of renal damage in COVID-19 patients. However, the underlying mechanisms and diagnostic approaches remain to be determined.
Methods: We interrogated the expression of virus-related host factors in single-cell RNA sequencing (scRNA-seq) datasets of normal human kidneys and kidneys with pre-existing diseases. We validated the results with immunohistochemistry and urinary proteomics of COVID-19 patients and healthy individuals. We also assessed the effects of genetic variants on kidney susceptibility using expression quantitative trait loci (eQTLs) database.

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

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

Funding: Government Support - Non-U.S.

SA-OR02
Selective Tropism of SARS-CoV-2 in Genome-Edited Kidney Organoids Reveals Nephropathic and Therapeutic Effects
Louisa Helms, Benjamin A. Julier, Jonathan Himmelbarf, Benjamin S. Freedman. University of Washington, Seattle, WA.

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

Methods: Kidney organoids were differentiated from control, PKD2+, or ACE2+ stem cells, and infected with WA1/2020 SARS-CoV-2 mNeonGreen transgene. Organoids were infected under BSL3 conditions with supernatant collected for plaque assays and analyzed with immunofluorescence or RNA was extracted. Remdesivir was added post-infection, or novel engineered LCBI Spike binder proteins were pre-incubated with SARS-CoV-2 prior to infection.

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

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

Funding: Other U.S. Government Support

SA-OR03
The Spike Protein of the Causative COVID-19 Virus Induces Heme Oxygenase-1: Pathophysiologic Implications
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Background: Acute kidney injury (AKI) is both a consequence and determinant of outcomes in COVID-19. The kidney is one of the major organs infected by the causative virus SARS-CoV-2. The spike protein of SARS-CoV-2 is required for viral entry into cells and is present in the urine of patients with COVID-19 and AKI. The present study examined cellular effects that result from transfecting the spike protein of SARS-CoV-2 in HEK293 kidney cells.

Methods: HEK293-AE2+ cells stably overexpressing ACE2 were used. Codon optimized pcDNA encoding SARS-CoV-2 spike (7788bp) or empty vector (4033bp) plasmid was transfected using Lipofectamine LTX. For studies examining the effect of quercetin (an inducer of heme oxygenase-1, HO-1), full media containing quercetin or vehicle was added at 4-6 hours post transfection. mRNA and protein expression was assessed by quantitative real-time RT-PCR and western blot respectively. Synecytium formation was assessed by acquiring phase contrast images using Olympus CK40 microscope and the area covered by syncytia was measured using ImageJ software.

Results: HEK293-AE2+ cells expressed SARS-CoV-2 spike protein upon spike transfection. Such expression led to synecytia formation, the sloughing of sheets of cells, and focal denudation of the cell monolayer. Spike protein expression upregulated potentially nephroprotective genes such as TNF-α, MCP-1, and ICAM1. Spike protein expression also upregulated potentially cytoprotective genes such as HO-1, as demonstrated by HO-1 mRNA and protein expression and relevant signaling pathways (p-Akt, p-STAT3, and p-p38) involved in inducing the HO-1 gene. Quercetin, a naturally occurring compound that induces HO-1, markedly reduced synecytia formation and spike protein expression.

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

Funding: NIDDK Support

SA-OR04
A Novel Soluble ACE2 Protein Protects from Lethal SARS-CoV-2 Infection
Luise Hassler,1 Jan Wysocki,1 Ian A. Gelarden,1 Anastasia Tomatisidou,2 Haley Gula,2 Vlad I. Nicolaescu,3 Glenn Randall,2 Anjana Yeldandi,2 Daniel Battle,1 Northwestern University Feinberg School of Medicine, Chicago, IL; 1University of Chicago, Chicago, IL.

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

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

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

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

Funding: Private Foundation Support
SA-OR05

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

Stefania Affatato,1 Federica Mescia,1 Virginia Quaresima,2 Chiara Fiorini,2 Mario Gaggiotti,2 Nicola Bossini,2 Paola Gaggia,2 Raffaele Badolato,1 Luigi D. Notarangelo,3 Marco Chiariini,2 Francesco Scolari,1 Federico Alberici,1

1Università degli Studi di Brescia, Brescia, Italy; 2Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Brescia, Italy; 3National Institute of Allergy and Infectious Diseases Laboratory of Clinical Immunology and Microbiology, Bethesda, MD.

Background: Mortality for COVID-19 in dialysis (HD) and kidney transplant (TX) patients (pts) is 30%. In these pts the immunology of the disease has been poorly explored.

Methods: 32 HD or TX pts hospitalized for COVID-19 (COV), of which 13 with benign course (PosCOV) and 19 who died or developed ARDS (NegCOV), 10 controls (HC) and 12 HD/TX without COVID-19 (PC), have been included. Lymphocytes subsets, dendritic cells (DC) and monocytes activation (MA) have been explored.

Results: COV showed lower counts of CD4+, CD8+, CD56+, CD19+, DC and higher counts of terminally differentiated CD19+ compared to HC and PC; CD4+, CD8+, CD19+ and MA were significantly lower in NegCOV than PosCOV. Compared to HD, TX showed lower CD56+, pDC and MA.

Conclusions: The COV group showed immunological alterations compared to HC and PC with deeper alterations of the innate immune system in TX pts with COVID-19.

SA-OR06

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

Ayman Al Jurdi,1,2 Rodrigo Benedetti Gassen,1 Thiago J. Borges,1 Frank E. Hulicke,1 Isadora T. Lape,1 Orhan Efe,1,3 Areej saud a Alghamdi,3 Pojan Patel,1 John Y. Choi,1 Zhabiz Solhjou,1 Camille Kotton,1 Jamil R. Azzi,1,2 Leonardo V. Riella.1

1Massachusetts General Hospital, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3Boston Children’s Hospital, Boston, MA.

Background: There is limited data on the safety and efficacy of SARS-CoV-2 mRNA vaccines in kidney transplant recipients (KTRs).

Methods: We conducted a prospective, multi-center study of 58 adult KTRs receiving mRNA-BNT162b2 or mRNA-1273 vaccines to assess vaccine safety and efficacy. Primary outcome was biopsy-proven rejection within 3 months of vaccination. Secondary outcomes included adverse events, serum creatinine, proteinuria, donor-derived cell-free DNA (ddcDNA) levels, and antibody and cellular immunity generation against SARS-CoV-2.

Results: Median age was 62 with 41% females. Median time post-transplantation was 48 months. Only one patient (2%) developed acute cellular rejection though patient had been recently converted to belatacept. There were no severe adverse events or deaths during follow-up. Two patients (3%) developed SARS-CoV-2 infection, one of whom required hospitalization. There was no significant change in serum creatinine, proteinuria or ddcDNA during the study. Following vaccination, 36%, 25% and 20% of KTRs developed anti-spike, anti-S1 and anti-RBD antibodies. KTRs with anti-spike and anti-RBD antibodies had a neutralizing response, compared to 44% in KTRs with anti-spike but without anti-RBD antibodies (RR 2.25, 95% CI 1.08-4.67). There was a significant increase in IFN-gamma spots per 10⁶ PBMCs incubated with S1 peptides following vaccination (p=0.0143).
Methods: Between March and August 2020, we completed 1601 unique IRB-approved COVID-19 assessment surveys. The survey covered COVID-19 symptoms, exposure risk, PCR and/or serology testing, and hospitalization. 298 of those patients were exome sequenced. We analyzed differences in COVID-19 PCR, serology and hospitalization rate and genetic analysis to identify possibly associated variants in the immune/coagulation pathways, suggested to be involved in COVID-19 susceptibility/severity by recent publications. We also analyzed variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines for clinical annotation of genetic results.

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

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

SA-OR07
SARS-CoV-2 Vaccine Impact on COVID-19 Incidence in Maintenance Dialysis Patients
Eduardo K. Lacson,1,2 Harold J. Manley,3 Gideon N. Aweh,3 Vladimir Ladik, Jill M. Frantzen,3 Caroline M. Hsu,4 Dana Miskulnii,5 Daniel E. Weiner,4 Doug Johnson.1 1Diagnosis Clinic Inc, Nashville, TN; 2Tufts Medical Center, Boston, MA.

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

Methods: All adult maintenance dialysis patients prior to COVID-19 treated by Dialysis Clinic, Inc. who received one dose of vaccine were classified as “partially vaccinated” and at 14+ days after completing the manufacturer recommended series were classified as “fully vaccinated”; else were “unvaccinated”. During the study period from 2/1/21 to 5/19/21, all new test-confirmed COVID-19 cases were documented. Every day at-risk for each patient was assigned to vaccination status and contributed to the denominator. Case rates per 10,000 days at-risk were compared using logistic regression.

Results: Among 13,717 eligible patients contributing 1,426,187 days at-risk, 327 new COVID-19 occurred. Only 4% were in fully vaccinated patients, with 25% in partially vaccinated and 70% in unvaccinated patients. Unvaccinated patients had 10-fold higher risk of COVID-19 than fully vaccinated patients (Table). Only 3 of 13 (23%) breakthrough cases were symptomatic, and 1 of 13 (8%) was hospitalized for COVID-19. In contrast, 67 (29%) of unvaccinated and 14 (40%) of partially vaccinated patients were hospitalized for COVID-19, with 6 and 2 deaths, respectively.

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

SA-OR09
APOL1 Risk Variants, AKI, and Death in Black Veterans with COVID-19
Adriana Huang,1,2 Shalija C. Shah,4,5 Alexander Bick,1,2 Zhihong Yu,1,2 Hua-Chang Chen,1,2 Ran Tao,1,2 Elvis A. Akwo,1,2 Cecilia P. Chung,1,2 Michael E. Matheny,1,2 Katalin Susztak,2 Cassianne Robinson-Cohen,2 Sony Tuteja,2 Edward D. Siew,1 Million Veteran Program ‘Vanderbilt University Medical Center, Nashville, TN; ‘Nashville VA, Nashville, TN; ‘University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ‘University of California San Diego, La Jolla, CA; ‘San Diego VAMC, San Diego, TN.

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

Methods: We performed a retrospective study of 999 Black patients in the VA Million Veteran Program hospitalized with COVID-19 between March 2020 and January 2021. The primary exposure was having 2 APOL1 risk variants (APOL1 high-risk group), compared to having 1 or 0 risk variants (APOL1 low-risk group). The primary outcome was AKI. The secondary outcomes were AKI severity stages and death. We performed a subgroup analysis in individuals with eGFR ≥ 60 ml/min/1.73m2.

Results: 392 (39.6%) patients developed AKI, 28 (7%) required dialysis and 122 (12.3%) died. Patients categorized as APOL1 high-risk group had a significantly higher risk of AKI compared to patients with 1 or 0 risk variants (APOL1 low-risk group). The primary outcome was AKI. The secondary outcomes were AKI severity stages and death. We performed a subgroup analysis in individuals with eGFR ≥ 60 ml/min/1.73m2.

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

SA-OR08
Genetic Findings in COVID-19-Positive Patients from a Cohort of Kidney and Liver Patients at Columbia University

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

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

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

SA-OR05
Genetic Findings in COVID-19-Positive Patients from a Cohort of Kidney and Liver Patients at Columbia University

Background: Patients with preexisting chronic kidney (CKD) and liver disease and liver are more at risk from COVID-19, but reasons for variability in disease susceptibility and severity is still poorly understood. Given the high infection rate in New York City, we conducted a COVID-19 assessment survey in a cohort of CKD and liver patients previously consented into genetic studies.
SA-OR10
Neutrophil Extracellular Traps and Endothelial Injury in COVID-19 Associated AKI
Naomi Pode shakked,1, 2 Brandon M. Henry,1 Stefanie W. Benoit,1, 2 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 1University of Cincinnati College of Medicine, Cincinnati, OH.

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

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

Results: 51 patients were enrolled, median age 50.5 years (IQR 41-66). Age, race, coronary artery disease, heart failure, chronic kidney disease, and chronic liver disease were associated with severe AKI, while hypertension was protective. cfDNA levels were higher in those who developed severe AKI (p<0.001) and needed RRT (p=0.020) during hospitalization. cfDNA positively correlated with SCr, NGAL, cystatin C, neutrophil count, neutrophil-to-lymphocyte ratio, CTSa, C5a, Scrb-5, IL-6, IL-8, IL-10, TNF-α, LDH, CRP, ferritin, fibrinogen, and negatively correlated with ADAMTS13/VWF ratio and lymphocyte count. In the multivariable logistic regression model adjusted for age, comorbidities, and SCr, one unit increase in cfDNA value was associated with a 4.6% increased odds of severe AKI (OR=1.046; p=0.040). Diagnostic performance of cfDNA is shown in Table 1.

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

Diagnostic Performance of cfDNA for COVID-19 AKI

<table>
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<tr>
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</tbody>
</table>

SA-OR11
Identification of Molecularly Distinct Sub-Phenotypes in AKI and Association with Long-Term Clinical Outcomes
Pavan K. Bhattacharya,1 David K. Prince,2 Sherry Mansour,3 Talat Alp Ikizler,1 Edward D. Siew,1 Amit X. Garg,4 Alan S. Go,5 James S. Kaufman,5 Paul L. Kimmel,7 Steven G. Coca,3 Chirag R. Parikh,3 Mark M. Wurfel,1 Jonathan Himmelfarb,8 Yale University, New Haven, CT; 2Yale University, New Haven, CT; 3Vanderbilt University, Nashville, TN; 4Western University, London, ON, Canada; 5University of California San Francisco, San Francisco, CA; 6University of Pennsylvania, Philadelphia, PA; 7Regents of the University of Minnesota, Minneapolis, MN; 8University of Illinois at Chicago, Chicago, IL; 9Cleveland Clinic, Cleveland, OH; 10The MetroHealth System, Cleveland, OH; 11Wayne State University School of Medicine, Detroit, MI; 12Tulane University School of Medicine, New Orleans, LA; 13Kaiser Permanente, Oakland, CA; 14Johns Hopkins University, Baltimore, MD.

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

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

Results: Among 769 AKI patients both LCA and k-Means clustering identified two AKI sub-phenotypes. Class 1 was characterized by a higher prevalence of prior congestive heart failure and favorable blood inflammatory and urinary tubular injury biomarkers, while class 2 was characterized by higher rates of prior chronic kidney disease and less favorable biomarkers. After a median follow-up of 4.7 years, the risk for MAKE was higher with class 2 (HR 1.8, 95% CI 1.08 to 1.84) compared with class 1 adjusting for demographics, hospital level factors and KDIGO Stage of AKI. The higher risk of MAKE among class 2 was explained by a higher risk of chronic kidney disease progression and dialysis (Figure 1).

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

Funding: NIDDK Support

SA-OR12
Association of Mild-to-Moderate AKI with CKD Progression Among Individuals with CKD: The CRIC Study
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Background: Observational studies have suggested that even mild episodes of AKI have a large effect on accelerating CKD progression (EJ See et al 2019;95:160-172). These seem inconsistent with clinical trials in which reducing AKI rate did not translate into reducing CKD risk (AX Garg et al JAMA 2014: 311:2191-8, 8G Coca et al JASN 2016; 27: 2529-42). These differences may be due to incomplete control of important confounders such as proteinuria since proteinuria is both a strong risk factor for development of AKI and CKD progression.

Methods: To better address potential residual confounding, including confounding by pre-AKI proteinuria and pre-AKI eGFR slope, we quantified the independent association between an episode of mild-to-moderate AKI (identified using inpatient SCR measurements and staged using KDIGO guidelines) on eGFR trajectory during follow-up of 4.7 years. eGFR trajectory was determined using outpatient protein protocol measurements in the prospective Chronic Renal Insufficiency Cohort (CRIC).

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

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

Funding: NIDDK Support

SA-OR13
Evidence for Kidney Involvement in an Acute Graft vs. Host Disease Model of Allogeneic Stem Cell Transplant (HSCT) in Non-Human Primates
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Background: Kidney injury is increasingly recognized as a significant cause of morbidity and mortality in recipients of HSCT. The frequency of kidney injury can be as high as 73% and among patients with kidney injury who require dialysis, mortality...
approaches 100%. Acute graft-versus-host disease (aGVHD) has emerged as an important risk factor for chronic graft-versus-host disease (cGVHD). Both aGVHD and cGVHD patients but whether the kidney is affected is a feature of aGVHD has not been established. In this study and utilizing a non-human primate model of HSCT we tested the hypothesis that the kidney undergoes inflammatory changes consistent with aGVHD.

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

**Results:** As expected control kidneys had normal renal histology. In contrast, kidneys from allo-HCT recipients had evidence of mesangiolysis and tubulitis. By IHC we determined increased expression of CD68+ monocyte lineage cells, Granayne B+ cytotoxic T lymphocytes and CD3+ T lymphocytes. There was no difference in the expression of CD3+ NK cells while the number of CD20+ B lymphocytes was lower in allo-HCT as compared to controls.

**Methods:** The studies demonstrate that aGVHD results in renal injury characterized by tubulitis and mesangiolysis and linked to increased infiltration by monocytes and T lymphocytes. These findings suggest that the kidneys are a target of aGVHD and may explain the high frequency of acute kidney injury post allo-HCT.

**Funding:** NIDDK Support

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**SA-OR14**

**Serial Intravital Imaging of Ischemia-Reperfusion Injury Reveals the Dynamics of Tubular Injury and Repair**


**Background:** The kidney has a remarkable capacity to recover from acute kidney injury (AKI) but the cellular dynamics of cellular damage and repair are incompletely understood. In this study, we investigated ischemia-reperfusion injury (IRI)-induced proximal tubule (PT) cell death and proliferation of the same renal cells over time using serial intravital 2-photon microscopy (2PM).

**Methods:** We performed 21 minutes IRI of the left kidney followed by abdominal imaging window implantation for serial imaging of the same tissue at 1 h and day 1, 2, 3, 4, 7, 14 and 21 after IRI. CycB1-GFP reporter mice identified proliferating cells by GFP-expression in S2-G2-M cell cycle stages.

**Results:** Necrotic tubular cell death, as detected by Propidium Iodide (PI)-staining, was primarily observed 1 h post IRI and mostly affecting PTs with 10.1±4.1%, 12.3±3.8% and 1.9±0.8% PI-positive nuclei per S1, S2 and distal tubule (DT) collecting duct (CD) segments (Mean±SEM, n=8 each). From day 1, injured PTs shedded brush border contents, which correlated with epithelial flattening and onset of proliferation (p<0.05, r²=0.39). Tubular proliferation started day 1, peaked day 3 and was highest in S2 segments with 2.7±2%, 12.4±8% and 0.3±0.9% (Mean±SEM, n=8 each) of FP-positive nuclei per S1, S2 and DT/CD segments (p<0.02, vs. S2 and p<0.001 vs S2 and DT/CD). While in S1 segments proliferation derived mainly from surviving cells in immediate proximity to PI-positive cells, in S2 segments also cells further distant from injured sites proliferated. We observed shedded cytosolic content from injured PT regions flowing downstream into previously PI-negative PTs, which spatially coincided with their proliferation one day after the appearance of shedded material in the lumen. By day 4, several PT segments revealed severe cast formation and epithelial vacuolization with nuclear karyolysis. 75% of the vacuolized tubule population reached full recovery before day 14 post IRI, while the remaining 25% failed to recover, resulting in nephron loss.

**Conclusions:** This is the first study to track IR-induced injury and regeneration in the same renal cells over time. Our data uniquely links initial tissue damage to regenerative capacity of the renal PT in AKI and suggests distinct mechanisms for initiation of PT proliferation in S1 and S2 segments.

**Funding:** Private Foundation Support

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**SA-OR15**

**Genetic Validation of Hdac8 as a Therapeutic Target for AKI**

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**Background:** We previously identified 4-phenoxybutibatric acid (PTBA), which enhances kidney regeneration, and showed that histone deacetylase 8 (Hdac8) is a target of PTBA. Here, we show that loss of genetic deacetylation of Hdac8 protects against AKI in zebrafish, human kidney organoid and mouse models, and that Hdac8 mediates the efficacy of PTBA.

**Methods:** 

- **Hdac8** and wild type zebrafish were injected with gentamicin to induce AKI and followed. 
- The rats were treated with HDAC inhibitors and evaluated for survival, tubular proliferation, DNA damage response, and apoptosis with EdU, H2AX, and TUNEL staining, respectively. Tamoxifen treated male UB-CRERT2; Hdac8<sup>fl/fl</sup> (Hdac8 KO) were evaluated over 28 days after severe ischemia reperfusion aGVHD (IR-AKI) as compared to controls. 
- Methods: We used motif enrichment, trajectory, drug response pattern and cell-cell interaction analyses to define key drivers of failed and successful regeneration, finally informing in vivo experiments with 2 small molecules effectively ameliorating maladaptation.

**Results:** Loss of Hdac8<sup>fl/fl</sup> reduced severity of injury and improves repair in models of AKI. Studies in Hdc<sup>fl/fl</sup> mutants using sub-therapeutic doses of UPHD25 indicate that PTBA efficacy is mediated in AKI via Hdc8. Increased H2AX expression from kidney injury syndrome (KIS) suggests that Hdac8 and zebralins preferentially utilizes mechanisms of DDR for repair. These data provide strong genetic evidence that Hdac8 is a valid therapeutic target for AKI; mediates PTBA effects; and suggest a potential mechanism by which Hdac8 deletion induces productive repair.

**Funding:** NIDDK Support

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**SA-OR16**

**Loss of Proximal Tubular Krüppel-Like Factor 15 Is in Kidney Injury Is Essential for Repair and Reversion of Fatty Acid Oxidation**

Sian Preet, Ahmed A. Attallah, Yiqing Guo, Nehaben A. Gujarati, Sandeep K. Mallipautu. Stony Brook University, Stony Brook, NY.

**Background:** Loss of fatty acid oxidation in the proximal tubule (PT) is a critical mediator of acute kidney injury (AKI) and eventual fibrosis. The transcription factor PPARα is a key regulator of fatty acid oxidation (FAO); however, Ppara knockout mice do not have kidney injury at baseline, suggesting that other important regulators remain to be described. Krüppel-like factor 15 is expressed in PT, downregulated in AKI, and with PPARα, regulates FAO in cardiomyocytes. Our aim was to investigate the role of PT KLF15 in AKI and fibrosis.

**Methods:** PT-specific Klf15 knockout (Klf15<sup>−/−</sup>) mice were generated by breeding Klf15<sup>−/−</sup> and Pepck-Cre mice. Kidney injury was induced using the PT-specific DNA damaging agent aristolochic acid I (AAI) or by ischemia-reperfusion (IR). Blood was collected for serum biochemistry, and kidneys harvested for histological and IHC analyses to define key drivers of failed and successful regeneration, finally informing in vivo experiments with 2 small molecules effectively ameliorating maladaptation.

**Results:** Tamoxifen treated male UB-CRERT2; Klf15<sup>−/−</sup> mice subjected to AAI or IR showed higher levels of Klf15<sup>−/−</sup> mice subjected to AAI or IR had significantly worse injury than Klf15<sup>−/−</sup> mice, as assessed by higher serum creatinine and urine nitrogen levels, exacerbated histopathological features, more extensive loss of mature PT brush borders, and increased fibrosis. Klf15<sup>−/−</sup> mice showed higher levels of Klf15<sup>−/−</sup> mice showed lower levels of Krüppel-like factor 15 was expressed in PT, downregulated in AKI, and with PPARα, regulates FAO in cardiomyocytes. Our aim was to investigate the role of PT KLF15 in AKI and fibrosis.

**Results:** PT KLF15 expression was downregulated in response to injury in control mice. Klf15<sup>−/−</sup> mice subjected to AAI or IR had significantly worse injury than Klf15<sup>−/−</sup> mice subjected to AAI or IR had significantly worse injury than Klf15<sup>−/−</sup> mice, as assessed by higher serum creatinine and urine nitrogen levels, exacerbated histopathological features, more extensive loss of mature PT brush borders, and increased fibrosis. Klf15<sup>−/−</sup> mice showed higher levels of uptake of palmitate in FAO. KLF15 expression is positively correlated with eGFR and Ppara expression in human kidney biopsies with CKD.

**Conclusions:** PT KLF15 is a key regulator of AKI, and loss of KLF15 in kidney injury is detrimental through compromised FAO.

**Funding:** NIDDK Support, Veterans Affairs Support

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**SA-OR17**

**Single-Cell Transcriptomics Reveal Pyroptosis and Ferroptosis Inhibition Ameliorate Maladaptive AKI-to-CKD Progression and Reversion**

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**Background:** Following acute kidney injury (AKI) renal repair is possible to a certain extent. However, maladaptation to AKI leads to progression towards chronic kidney disease (CKD). Unwiring the incompletely understood processes driving both progression and repair might identify therapeutic targets to halt or reverse AKI-to-CKD progression.

**Methods:** Here we profiled transcriptomic changes at single-cell level over time in acutely injured kidneys of mice subjected to mild and severe bilateral ischemic reperfusion injury (IRI), modeling repair and maladaptation, respectively. Kidney function, tissue, bulk and single-cell gene expression analyses were performed 1, 3 and 14 after ischemia. We used motif enrichment, trajectory, drug response pattern and cell-cell interaction analyses to define key drivers of failed and successful regeneration, finally informing in vivo experiments with 2 small molecules effectively ameliorating maladaptation.
Results: Long bilateral ischemia resulted in sustained renal failure (1-14d) and severe maladaptive damage at 14d (CKD). AKI patients are at more than twice the increased risk of progressive CKD that leads to excess morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available. Peritubular capillary beds are significantly damaged during many types of AKI, which is closely associated with the transition to CKD progression. Vascular endothelial growth factor (VEGF) is a well-defined angiogenic factor via its major receptor, VEGF receptor 2 (VegfR2). However, prior work from others demonstrated a role of VEGF as a negative regulator of pericyte function and vessel maturation. The functional implications of the VegfR2 signaling in renal interstitium remains poorly understood.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of VegfR2 with constitutively expressed Foxd1-Cre (VegfR2RSC-/-) as well as tamoxifen inducible Foxd1-Cre (VegfR2RSCi-/-) to interrogate timing specific role of VegfR2 in renal interstitial cells in AKI-to-CKD. AKI/CKD models induced either by a renal ischemia/reperfusion injury (IRI) model or by low/dose repeated treatment of cisplatin were performed. Mice are monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis. Renal blood flow was evaluated with arterial spin-labeling MRI (ASL-MRI).

Results: We found that VegfR2RSC-/- mice have (I) reduced vascular injury and better blood flow post AKI, (II) are protected against AKI, and (III) have reduced AKI-to-CKD progression after renal IRI. Consistently, VegfR2RSCi-/- are protected against progression to CKD in a cisplatin AKI-to-CKD model. Mechanistically, it appears that the VegfR2RSCi-/- mice downregulate a maladaptive proliferation factor for pericytes, Thrombospondin-1 (TSP1). AKI triggers enhanced differentiation of a subpopulation of CD31+/ Foxd1+ cells, presumably caused by partial endothelial-mesenchymal transition (Endo-MT). Further, VegfR2RSC-/- mice are significantly protected against renal IRI.

Conclusions: These data suggest that VegfR2 signaling in renal interstitial cells exacerbates renal IRI and its post-AKI CKD progression as well as cisplatin AKI.

Funding: NIDDK Support

SA-OR18
VEGF-R2 Signaling in Renal Interstitium Exacerbates Post-AKI CKD Progression
Takuto Chiba, Sunder Sims-Lucas. University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: A dire consequence of acute kidney injury (AKI) is progression to chronic kidney disease (CKD). AKI patients are at more than twice the increased risk of progressive CKD that leads to excess morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available. Peritubular capillary beds are significantly damaged during many types of AKI, which is closely associated with the transition to CKD progression. Vascular endothelial growth factor (VEGF) is a well-defined angiogenic factor via its major receptor, VEGF receptor 2 (VegfR2). However, prior work from others demonstrated a role of VEGF as a negative regulator of pericyte function and vessel maturation. The functional implications of the VegfR2 signaling in renal interstitium remains poorly understood.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of VegfR2 with constitutively expressed Foxd1-Cre (VegfR2RSC-/-) as well as tamoxifen inducible Foxd1-Cre (VegfR2RSCi-/-) to interrogate timing specific role of VegfR2 in renal interstitial cells in AKI-to-CKD. AKI/CKD models induced either by a renal ischemia/reperfusion injury (IRI) model or by low/dose repeated treatment of cisplatin were performed. Mice are monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis. Renal blood flow was evaluated with arterial spin-labeling MRI (ASL-MRI).

Results: We found that VegfR2RSC-/- mice have (I) reduced vascular injury and better blood flow post AKI, (II) are protected against AKI, and (III) have reduced AKI-to-CKD progression after renal IRI. Consistently, VegfR2RSCi-/- are protected against progression to CKD in a cisplatin AKI-to-CKD model. Mechanistically, it appears that the VegfR2RSCi-/- mice downregulate a maladaptive proliferation factor for pericytes, Thrombospondin-1 (TSP1). AKI triggers enhanced differentiation of a subpopulation of CD31+/ Foxd1+ cells, presumably caused by partial endothelial-mesenchymal transition (Endo-MT). Further, VegfR2RSC-/- mice are significantly protected against renal IRI.

Conclusions: These data suggest that VegfR2 signaling in renal interstitial cells exacerbates renal IRI and its post-AKI CKD progression as well as cisplatin AKI.

Funding: NIDDK Support

SA-OR19
Immune Cells as Drivers of Kidney Myofibroblast Formation and Fibrosis After Acute Cardiac Dysfunction
Kevin G. Burfeind,1 Yoshio Funahashi,2 Adam C. Munhall,3 Mahaba B. Eiwa,3 Michael Hutchens,1 Oregon Health & Science University, Portland, OR; Portland VA Medical Center, Portland, OR.

Background: Acute kidney injury (AKI) is a cause of chronic kidney disease (CKD). AKI is a potential driver for early intervention to prevent CKD. Myofibroblast formation is a hallmark of CKD. We have performed extensive mechanistic investigation in a translational model of AKI-CKD transition, cardiac arrest and cardiopulmonary resuscitation (CA/CPR), in which all animals develop CKD at 7 weeks. The purpose of this study was to identify potential immune drivers of myofibroblast formation.

Methods: Cardiac arrest was induced with potassium chloride in anesthetized mice. Kidney single nuclear RNA sequencing (snRNASeq) revealed several distinct populations of kidney cells (Fig. 1E). High resolution subclustering combined with CellChat identified significantly upregulated interaction networks between immune cells and mesenchymal cells, including CD226 and CD96 signaling (Fig. 1E and F).

Conclusions: Monocytes and natural killer cells increased in the kidney after CA/CPR (Fig. 1B). PDGFRB+ cells increased at 7 days (Fig. 1C), and immune cells colocalized with aSMA+ myofibroblasts after CA/CPR (Fig. 1D). snRNASeq revealed several TFs as novel potential drivers of AKI-to-CKD progression upstream of inflammasome effectors. Additionally, in cell-cell interaction analyses we show how PT cells acquire an epithelial-to-immune phenotype during maladaptation. Finally, prompted by analyses of drug response transcriptional changes we show that inhibition of pyroptosis (VX765) and ferroptosis (liproxstatin) in vivo normalized single-cell transcriptomic kidney signatures despite severe IRI.

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

SA-OR20
Differential Role of Endothelial Prolyl-Hydroxylase 1, 2, 3 in AKI
Ratnakar Tiwari, Si Young An, Pinlopri P. Kaptisino. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Recently, we showed that pre-ischemic inhibition of endothelial cell (EC)-HIF Prolyl Hydroxylase 2 (Phd2) protects against kidney ischemia-reperfusion injury (IRI). However, the role of post-ischemic inactivation of EC-Phd2 in kidney repair remains unclear. Further, recent single-cell RNA sequencing (scRNA-seq) data suggest a role for other EC-Phd isoforms (EC-Phd1 and EC-Phd3) in oxygen sensing. Here, we wished to address the role of post-ischemic inactivation of EC-Phd1, EC-Phd2, and EC-Phd3 in kidney repair.

Methods: Post-ischemic inactivation of EC-Phd1 (EC-Phd1ko), Phd2 (EC-Phd2ko), and Phd3 (EC-Phd3ko) was achieved by the Cdh5(P AC)CreER inducible system. To avoid compensatory effects between Phds, we generated mice with concurrent deletion of EC-Phd1, 2, and 3 (EC-Phd123ko) and induced recombination after IRI. Analysis was performed on day 14 post-IRI.

Conclusions: CA/CPR induces acute and lasting renal inflammation, which correlates with myofibroblast expansion. Lympocytes communicate with myofibroblast precursors, revealing potential therapeutic targets.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: Post-ischemic inactivation of EC-Phd1 or EC-Phd2 failed to protect kidneys based on mRNA expression of kidney injury molecule 1 (Kim1) and profibrotic genes lysyl oxidase-like 2 (Loxl2), transforming growth factor-beta 1 (Tgfb1), and smooth muscle actin (Acta2) and histopathological analysis (n=7–8). Surprisingly, the inactivation of EC-Phd3 following IRI exacerbated kidney damage and fibrosis as indicated by increased expression of Kim1, Tgfb1, and Acta2 and deposition of collagen (n=6–8, p<0.05). Likewise, post-ischemic concurrent deletion of EC-Phd2.13 increased kidney damage and fibrosis assessed by histopathological analysis and increased expression of profibrotic genes and collagen deposition (n=7–8, p=0.05, respectively, compared to Cre-controls). These changes were associated with significant worsening of renal function assessed by blood urea nitrogen level and transdermal GFR measurements (n=7, p<0.05). scRNA-seq data of the EC-Phd123 post-ischemic kidneys showed significant transcriptional alterations in the EC cluster compared to Cre-controls with prominent changes in metabolic genes. Significant transcriptional changes were also observed in tubular, fibroblast, and inflammatory cell clusters between the two genotypes.

Conclusions: Post-ischemic concurrent inactivation of Phd1, 2, and 3 significantly impaired renal function, induced fibrosis which was mainly driven by EC-Phd3 inactivation. We delineated a critical role for EC-Phd3 in post-ischemic AKI repair.

Funding: NIDDK Support

SA-OR21
Finereneone and Kidney Outcomes in Patients with CKD and Type 2 Diabetes

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Background: In the FIGARO-DKD trial, finereneone reduced the risk of kidney outcomes in patients with predominantly advanced chronic kidney disease (CKD) and type 2 diabetes (T2D). FIGARO-DKD investigated the effects of finereneone in patients with less advanced CKD and T2D. The primary outcome of FIGARO-DKD was a cardiovascular composite; here we report the secondary kidney outcomes.

Methods: FIGARO-DKD (NCT02545049) was a randomized, double-blind, placebo-controlled phase III trial. Patients with T2D, urine albumin-to-creatinine ratio (UACR) ≥300–5000 mg/g and estimated glomerular filtration rate (eGFR) ≥25–90 mL/min/1.73 m², optimized renin-angiotensin system blockade, and screening serum potassium ≥4.8 mg/dL were randomized to finereneone or placebo. The key secondary kidney outcome was an event of composite (40%) at time to kidney failure, sustained ≥40% eGFR decline from baseline, or renal death. Another similar secondary composite endpoint, excluding a sustained ≥40% eGFR decrease with a ≥57% decrease, and change in UACR from baseline to month 4 were pre-specified outcomes in the hierarchical testing strategy.

Results: In the 7352 patients included in the analysis, 62% of patients had baseline eGFR ≥60 mL/min/1.73 m² and 49% had baseline UACR <300 mg/g. Over a median follow-up of 3.4 years, 350 (9.5%) patients treated with finereneone and 395 (10.8%) patients with placebo had a ≥40% eGFR composite endpoint event (hazard ratio [HR]=0.87, 95% confidence interval [CI] 0.76–1.01; p=0.069). There was a clinically meaningful prolongation of the time to the 57% eGFR composite endpoint with finereneone (HR=0.77, 95% CI 0.60–0.99). Greater reduction in UACR at month 4 was observed with finereneone (ratio of least-squares means 0.68, 95% CI 0.65–0.70). Overall, the incidence of adverse events were similar between treatment arms.

Conclusions: In FIGARO-DKD, patients with stage 1–4 CKD and T2D, finereneone induced a pronounced reduction in albuminuria. Kidney composite outcomes observed were directionally similar to that seen among patients with more advanced kidney disease in the FIGARO-DKD trial.

Funding: Commercial Support - Bayer AG

SA-OR22
Finereneone in Patients with CKD and Type 2 Diabetes by SGLT-2 Treatment: The FIDELITY Analysis

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Background: The aim of the FIDELITY analysis is to evaluate the efficacy and safety of finereneone, a novel, non-stereoidal, selective mineralocorticoid receptor antagonist, across the spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIGARO-DKD and FIGARO-DKD trials. Sodium-glucose co-transporter-2 inhibitors (SGLT-2Is) have been shown to decrease the risk of CKD progression, thus their combined use with finereneone is of interest. We report the pooled FIDELITY analysis of patients by SGLT-2 use.

Methods: This pre-specified analysis combines patient-level data from the FIGARO-DKD (NCT02545049) and FIGARO-DKD (NCT02545049) phase III, randomized, double-blind, placebo-controlled, multicenter clinical trials. Patients were randomized 1:1 to oral finereneone or placebo. Patients had T2D and either a urine albumin-to-creatinine ratio (UACR) ≥30–500 mg/g and estimated glomerular filtration rate (eGFR) ≥25–90 mL/min/1.73 m², or UACR ≥300–5000 mg/g and eGFR ≥25–90 mL/min/1.73 m², with optimized renin-angiotensin system blockade. Efficacy outcomes included a cardiovascular (CV) composite endpoint of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and a kidney composite endpoint of time to kidney failure, sustained ≥40% eGFR decline from baseline, or renal death.

Results: The FIDELITY analysis includes 13,026 patients. Approximately 7% of patients (n=877) received an SGLT-2 at baseline (finereneone: 6.7% [n=438]; placebo: 6.9% [n=439]). Compared with placebo, finereneone reduced the risk of any CV composite endpoint irrespective of SGLT-2 use at baseline (with SGLT-2: hazard ratio [HR]=0.63, 95% confidence interval [CI] 0.40–1.00; without SGLT-2: HR=0.87, 95% CI 0.79–0.96; p-interaction 0.41), additional findings for efficacy outcomes, in addition to overall safety and FIDELITY-coma-related events by SGLT-2 treatment, will be prespecified in the future. Conclusions: FIGARO-DKD and FIGARO-DKD comprise the largest cardiorespiratory outcomes program to date; therefore, combining the data for the SGLT2i subgroup in the FIDELITY analysis may provide further insights into the effects of receiving both finereneone and an SGLT-2.

Funding: Commercial Support - Bayer AG

SA-OR23
Sodium-Glucose Cotransporter 2 Inhibitors as Adjunct Therapy for Type 1 Diabetes and the Benefit on Cardiovascular and Renal Disease Evaluated by Steno Risk Engines

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Background: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have beneficial cardiovascular and renal effects in persons with type 2 diabetes but no studies have shown whether this can be demonstrated in type 1 diabetes (T1D). We aimed to estimate the risk of cardiovascular (CV) and end-stage kidney disease (ESKD) in persons with T1D with and without treatment with SGLT2i.

Methods: The study is based on 3,660 adults with T1D treated from 2001-2016 who fulfilled the inclusion criteria of age 30-75 years and an eGFR ≥50 mL/min/1.73 m². The Steno Type 1 Risk Engines was used to calculate 5-year cumulative risks of ESKD and in the subset of 3,284 (89.7%) without previous CVD at baseline, 5- and 10-year cumulative risk of CVD were estimated. The effect of SGLT2i was simulated by changing the recorded HbA1c and systolic blood pressure (SBP) values in accordance with results from the EMPACT T1D studies. In both the SGLT2i and placebo arms, change in HbA1c and SBP was simulated as randomly drawn numbers from a normal distribution with mean (standard deviation (SD)) of -3.6 (0.9) mmol/mol and -1.12 (2.8) mmHg. The recorded eGFR and albuminuria were changed in accordance with results from the Tandem studies; no change in eGFR and mean (SD) % change in albuminuria of -23.7 (12.9).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: The SGLT2i induced change in the risk variables translated into an overall 5-year CVD risk reduction of 6.1% (95%CI 5.9, 6.3), with up to 11.1% (10.0, 12.2) in the subgroup with albuminuria. Similar results were seen for the 10-year risk of CVD. For the estimated 5-year risk of ESKD, we found an overall relative risk reduction of 5.3% (5.1, 5.4) with up to 7.6% (6.9, 8.4) in the subgroup with albuminuria.

Conclusions: The STEMI T1 CVD and renal risk engine we estimated the risk of CVD and ESKD in persons with T1D and with and without treatment with SGLT2i and found a substantial CVD and ESKD risk reduction, especially in the subgroup with albuminuria. Our model provides an estimate of benefit that may balance the risks associated with use of SGLT2 inhibition in T1D.

SA-OR24
Renal Autologous Cell Therapy (REACT) for Type 2 Diabetic Kidney Disease: Preliminary Results with Renal Cortex Implantation

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Background: Diabetic Kidney Disease (DKD) is the leading cause of kidney failure in the United States. REACT in preclinical trials demonstrated stability and improved kidney function without adverse effects. We present the 12 month findings of an ongoing Phase II multicenter randomized clinical trial (RCT) evaluating autologous homologous cell therapy on DKD progression in patients with stages 3a-4 DKD.

Methods: In this label 1 RCT, 83 participants, 30-80 yrs, eGFR 20-50 ml/min/1.73m2 were randomized to either REACT or a control group of standard of care. All patients had a kidney biopsy with renal progenitor cell isolation and expansion by cGMP. The treated group received two cell implants into the kidney cortex at six-month intervals with cGMP guidance. The control received standard of care treatment (SoC) including maximized hypertension, diabetes and comorbidity management. The primary endpoint is change in eGFR. The current analysis compares the mean eGFR and UACR of patients in each group at 12 months.

Results: No difference in Hgb or Hba1c were present between groups at baseline or 12 months. Annualized mean eGFR increased and UACR decreased in the treatment group from time of first injection to 12 months (Table). Major bleeding complications occurred in 1% of each group following biopsy or cell injections. There were no cell-related adverse events.

Conclusions: Preliminary findings indicate implantation of progenitor REACT into the renal cortex in DKD is safe and improved annualized eGFR and UACR. Further data will follow completion of the study.

Funding: Commercial Support - Pro-Kidney

SA-OR26
Genome-Wide Association Study (GWAS) in the Million Veteran Program of Diabetic Kidney Disease (DKD) Highlights Biology of the Glomerular Basement Membrane (GBM) and Tubular Transporter in DKD

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Background: Diabetes is the most common cause of end-stage renal disease (ESRD) worldwide. Diabetic Kidney Disease (DKD) is defined by reduced kidney function and/or albuminuria. We here study the genetic determinants of DKD.

Methods: Our primary outcome was a composite of low estimated glomerular filtration rate (eGFR), or end-stage renal disease (ESRD). Cases had to meet criteria for diabetes for at least 5 years before the onset of ESKD, while controls had to meet diabetes criteria for at least 7 years without DKD. Our secondary outcome was proteinuria/macroalbuminuria, no specific diabetes duration was required for the proteinuria cases. We conducted a large GWAS in 50,355 participants (21,273 cases) of European ancestry, and 18,144 (7,700 cases) of Non-Hispanic Blacks. Cases and controls were re-registered onto additively coded genotypes imputed to a 10,000 Genomes panel, with MAF>1%, adjusting for model 1: age, sex and 10 race/ethnicity-specific principal components and model 2: median and HBA1c, BMI, and systolic blood pressure. Inverse-variance-weighted fixed-effects meta-analysis was conducted across race groups.

Results: Two loci reach genome-wide significance in the transethnic GWAS for low eGFR or ESRD: rs113795872 (CUBN, p=9.8E-14), and rs11149134 (UMOD, p= 3.761E-12). We replicated the association with the one variant in COL4A3 reported as associated with DKD r=55703767 (p=0.002). Five loci reach significant GWAS association with persistent gross proteinuria: CUBN (p=1.77E-25), UMOD (4.5E-14), CDCC158 (8.17E-10), SHROOM3 (6.69E-09), and CEBPB (1.5E-08).

Conclusions: Our study found 5 genome-wide significant associations with different manifestations of DKD. Some of the involved genes play a role as a component of the glomerular basement membrane or renal tubular function and may represent targets for therapy.

Funding: Veterans Affairs Support

SA-OR27
Urinary Complement Proteome and 10-Year Risk of ESKD in Diabetes

Salina Moon,1 Zaipul I Abedini,2 Simon T. Dillon,2 John H. M. Y. Looker,1 Eiichiro Satake,3 Anna L. Urinary Inflammatory Proteomics and 10-Year Risk of ESKD in Diabetes

L. S. Segal,5 Bijin Thajudeen,6,8 Z. I. Abedini,3 Simon T. Dillon,2 John H. M. Y. Looker,1 Eiichiro Satake,3 Anna L. Urinary Inflammatory Proteomics and 10-Year Risk of ESKD in Diabetes

Background: Our pilot urinary inflammatory proteomics identified enrichment in the Complement system in subjects with progressive diabetic kidney disease (DKD). Thus, we aimed to comprehensively evaluate the Complement proteome reflected by: (1) the urinary inflammatory proteomics; and (2) enrichment in the Complement system in subjects with progressive diabetic kidney disease (DKD). We here study the genetic determinants of DKD.

Methods: Our primary outcome was a composite of low estimated glomerular filtration rate (eGFR), or end-stage renal disease (ESRD). Cases had to meet criteria for diabetes for at least 5 years before the onset of ESKD, while controls had to meet diabetes criteria for at least 7 years without DKD. Our secondary outcome was proteinuria/macroalbuminuria, no specific diabetes duration was required for the proteinuria cases. We conducted a large GWAS in 50,355 participants (21,273 cases) of European ancestry, and 18,144 (7,700 cases) of Non-Hispanic Blacks. Cases and controls were re-registered onto additively coded genotypes imputed to a 10,000 Genomes panel, with MAF>1%, adjusting for model 1: age, sex and 10 race/ethnicity-specific principal components and model 2: median and HBA1c, BMI, and systolic blood pressure. Inverse-variance-weighted fixed-effects meta-analysis was conducted across race groups.

Results: Two loci reach genome-wide significance in the transethnic GWAS for low eGFR or ESRD: rs113795872 (CUBN, p=9.8E-14), and rs11149134 (UMOD, p= 3.761E-12). We replicated the association with the one variant in COL4A3 reported as associated with DKD r=55703767 (p=0.002). Five loci reach significant GWAS association with persistent gross proteinuria: CUBN (p=1.77E-25), UMOD (4.5E-14), CDCC158 (8.17E-10), SHROOM3 (6.69E-09), and CEBPB (1.5E-08).

Conclusions: Our study found 5 genome-wide significant associations with different manifestations of DKD. Some of the involved genes play a role as a component of the glomerular basement membrane or renal tubular function and may represent targets for therapy.

Funding: Veterans Affairs Support
quantitative immunoassays. We evaluated kidney tissue expressions of the Complement system with affinity proteomics in 23 subjects with an overt DKD and 10 controls. Results: 160 (43%) subjects developed ESKD in 10 years. Multiple Complement proteins were associated with ESKD risk in Bonferroni-adjusted Cox models (risk per tertile change of the top protein, C3a: HR 4.2, p=10^{-6}; Fig A). Cumulative 10-year risk for subjects with low levels of the top proteins built into Principal Component-based tertiles (PC) was 18%, vs. 78% for those with high levels (Fig B). Accuracy of biostatistical and machine learning models built on the top proteins ranged from c=0.85 to 0.87. Quantitative measurements correlated with proteomics measurements and our outcome (median CFH in ESKD progressors: 214 vs. non-progressors: 8 ng/ml; p<10^{-14}). Of the top 10 urinary Complement proteins, 5 had increased renal expressions in subjects with DKD compared to controls. Renal expression of C3a featured the highest fold change, and CFH had the most significant association (Fig C).

Conclusions: This study revealed robust associations of the urinary Complement protein with 10-year risk of ESKD in subjects with T1D and T2D, with select correspondence in kidney protein expressions. These findings strongly suggest that the Complement system is an important driver of DKD progression.

Funding: Other NIH Support - NIH R01 DK123459, Private Foundation Support

SA-OR28

Circulating Metabolites to Predict Renal Outcomes in CANVAS Type 2 Diabetes Mellitus Population

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Background: Albuminuria and eGFR are biomarkers for kidney disease progression but fail to explain all future risk. Additional biomarkers that better represent underlying disease pathophysiology may improve the prediction of progression from chronic kidney disease (CKD) to end stage renal disease (ESRD). We examined if baseline plasma metabolites predict renal outcomes in the Canagliflozin Cardiovascular Assessment Study (CANVAS) participants.

Methods: Plasma metabolites were assayed from a subset of the CANVAS study participants by HILIC-mass spectrometry using targeted assays. Forty-two metabolites were analyzed for association with the renal outcome (40% eGFR decline, end-stage kidney disease, or renal death) using Cox regression.

Results: We included 967 (22%) of the 4,330 CANVAS participants comprising 341 females (35%), mean age 63 ±8 years, and BMI 33 ±5 kg/m². All patients had T2DM with mean Hba1c 8.2 ±0.9%, eGFR 75.5 ± 18.3 mL/min/1.73 m², and median ACR (1Q, 3Q) 11.89 (6.5, 37.49). During a median follow-up of 5.6 years, 63 (6.5%) patients experienced a renal event. There were 10 metabolites significantly associated with the renal outcome (all P<0.05) when adjusted for age and gender (Figure) and treatment effect. In a fully adjusted model (age, gender, race, BMI, Hba1c, cholesterol, blood pressure, history of heart failure, baseline ACR and eGFR), arginine alone remained significant (P=0.01).

Conclusions: Lower baseline plasma arginine levels are independently associated with high risk for renal events in patients with T2DM.

Funding: Commercial Support - Janssen Research & Development, LLC

SA-OR29

Uremic Solutes Are Associated with Cardiovascular Death in Diabetic Kidney Disease

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Background: Cardiovascular disease (CVD) is a major cause of mortality among people with diabetic kidney disease (DKD). The pathophysiology of CVD in DKD is not explained adequately by traditional CVD risk factors. Three small molecular weight, uncharged uremic solutes, asymmetric and symmetric dimethylarginine (ADMA, SDMA) and trimethylamine-N-oxide (TMAO) have been linked to CVD in ESKD. These solutes may be markers of CV mortality in non-ESKD DKD, as well as DKD progression to ESKD.

Methods: Uremic solutes in plasma and urine were assayed by mass spectrometry from a random subcohort of 555 REGARDS Study participants with diabetes and eGFR <60 ml/min/1.73m² at study entry. Plasma concentrations and urine/plasma (U/P) ratios of each solute were tested for association with CV mortality (primary outcome), all-cause mortality and incident ESKD (secondary outcomes). Cox regression models estimated the hazard ratios (HR) per log, increment, adjusted for demographic and CVD risk factors, baseline eGFR and urine albumin to creatinine ratio (UACR).

Results: Mean (SD) baseline eGFR was 44 ± 12 ml/min/1.73 m², median (IQR) UACR was 32 (11, 203) mg/g. CV death, overall mortality and ESKD occurred in 120, 285 and 89 participants, respectively, during mean 6.2 years of follow-up. Higher plasma ADMA, and lower U/P ratios of all three solutes were associated with increased CV mortality (Table). Higher plasma concentrations and lower U/P ratios of all three solutes were significantly associated with all-cause mortality. Only higher plasma SDMA was associated with incident ESKD.

Conclusions: Higher plasma concentration and lower U/P ratio of ADMA were independently associated with CV and all-cause mortality in DKD. The strong associations of U/P ratios with CV mortality outcomes suggest a connection between renal clearance of uremic solutes and CVD pathogenesis.

Funding: NIDDK Support

Table 1. Association of plasma biomarkers and U/P ratios (per two-fold higher) with mortality and incident ESKD outcomes.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Continuous (log2)</th>
<th>Adjusted HR CV mortality (95% CI)</th>
<th>Adjusted HR all-cause mortality (95% CI)</th>
<th>Adjusted HR ESKD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMA</td>
<td></td>
<td>2.10 (1.07, 4.14)</td>
<td>2.79 (1.97, 4.33)</td>
<td>2.35 (1.66, 3.33)</td>
</tr>
<tr>
<td>SDMA</td>
<td></td>
<td>2.07 (1.38, 3.09)</td>
<td>1.53 (1.23, 1.90)</td>
<td>1.34 (1.17, 1.53)</td>
</tr>
<tr>
<td>UACR</td>
<td></td>
<td>1.09 (1.07, 2.09)</td>
<td>1.37 (1.07, 1.75)</td>
<td>1.26 (1.15, 1.39)</td>
</tr>
<tr>
<td>TMAO</td>
<td></td>
<td>1.38 (1.21, 1.57)</td>
<td>1.38 (1.21, 1.57)</td>
<td>1.38 (1.21, 1.57)</td>
</tr>
</tbody>
</table>
SA-OR30

Essential Branched-Chain Amino Acids and Ribonic Acid Are Associated with Cardiorenal Events in Type 1 Diabetes

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Background: Diabetic kidney disease and cardiovascular disease (CVD) remain the leading causes of morbidity and mortality in diabetes despite recent advances in treatment. Further understanding of the underlying pathophysiology is needed. We investigated associations between serum metabolites and cardiorenal events.

Methods: The study comprised of 637 individuals with type 1 diabetes and various degrees of albuminuria. Non-targeted serum metabolomics was performed using two-dimensional gas chromatography coupled to time-of-flight mass-spectrometry. Longitudinal data on combined cardiorenal events (coronary events, peripheral arterial interventions, stroke, eGFR decline ≥30%, end-stage kidney disease and all-cause mortality) were obtained from National Danish Health registries and analyzed by Cox proportional hazards models. Adjustments included sex, baseline age, HbA1c, mean arterial pressure, smoking, body mass index, statin treatment, p-triglycerides, total cholesterol, eGFR, albuminuria, previous CVD and correction for multiple testing by false discovery rate (FDR).

Results: Of the included participants, 55% were male and baseline mean age was 55 ± 13 years. 28% had macroalbuminuria, 25% microalbuminuria and 47% normoalbuminuria. The mean eGFR was 81 ± 26 ml/m^2/1.73m^2. A total of 75 metabolites were included in the analyses. Over a median (IQR) of 5.2 (4.8-5.7) years, 173 cardiorenal events were recorded. In adjusted analyses, ribonic acid was associated with a higher risk of cardiorenal events (HR 1.4, CI [1.2-1.8], p=-0.04). The essential branched-chain amino acids leucine (HR 0.8, CI [0.7-0.9], p=0.04) and valine (HR 0.8, CI [0.6-0.9], p=0.03) were associated with a lower risk of cardiorenal events.

Conclusions: In individuals with type 1 diabetes and various degrees of albuminuria, ribonic acid was associated with an increased risk of cardiorenal events and two essential branched-chain amino acids with a decreased risk, independently of relevant confounders. These findings might indicate important pathophysiology in the development of cardiorenal disease.

SA-OR31

Voclosporin Is Effective in Achieving Complete Renal Response in Severe Lupus Nephritis

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Background: Voclosporin is a novel calcineurin inhibitor with a favorable metabolic profile and a consistent dose-concentration relationship. The Phase 3 AURORA 1 trial demonstrated that compared to mycophenolate mofetil (MMF) and low-dose steroids, adding voclosporin significantly increased complete renal response (CRR) rates in patients with lupus nephritis (LN). We report the results of a post-hoc analysis evaluating the efficacy of voclosporin in patients with severe LN is similar to the overall population of AURORA 1.

Methods: Patients with systemic lupus erythematosus, biopsy-proven active LN (Class III, IV or V or III/IV), and proteinuria of ≥1.5 mg/mg (≥2 mg/mg for Class V) were eligible to enroll in AURORA 1. Overall, 179 and 178 patients were randomized to the voclosporin (23.7 mg BID) and control arms, respectively. All patients received MMF (1 g BID) and low-dose oral steroids. Severe LN was defined as baseline UPCR ≥3 mg/mg with Class III or IV biopsy (≥3 mg/mg) and severe LN is similar to the overall population of AURORA 1.

Results: There were 76 and 72 patients in the voclosporin and control arms, respectively, with severe disease. Mean (SD) UPCR at baseline was 5.9 (2.4) mg/mg (Table 1). CRR at one year was 34.2% and 11.5% in the voclosporin and control arms, respectively (odds ratio 4.43; p=0.001; Figure 1).

Conclusions: In patients with severe LN, adding voclosporin to MMF and steroids results in statistically significantly higher CRR rates. This is clinically meaningful given that patients with severe disease are at higher risk of worse long-term outcomes and development of ESKD.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.
SA-OR33
Antibodies Anti-Rituximab Do Not Affect Response to Rituximab in Idiopathic Nephrotic Syndrome
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Background: Previous studies showed how infusion of the chimeric anti-CD20 rituximab results in production of antibodies anti-rituximab, that may limit the efficacy of further infusions. Among other reasons, the reduced immunogenicity of fully humanized anti-CD20 antibodies should increase their efficacy. In a randomized clinical trial, we compared the efficacy of ofatumumab vs. rituximab in children and young adults with steroid dependent nephrotic syndrome. As secondary endpoints, we evaluated possible role of anti-CD20 rituximab.

Methods: We randomized 140 children treated with single infusion of rituximab or ofatumumab, with a follow up of 24 months. We measured anti-rituximab antibodies IgG at the enrolment in 64/140 (46%) patients who have previously received rituximab and at 6 months in patients in the rituximab arm. Median time of the previous rituximab was 36 (12-51) months before enrolment.

Results: As primary endpoint, ofatumumab was not superior to rituximab in maintaining remission (Fig 1a). Serum anti-rituximab IgG were undetectable at baseline in 64 participants who had previously received rituximab. Six months following rituximab infusion, anti-rituximab antibodies levels increased in 14 (42%) of the 33/64 patients who were randomized in the rituximab arm (Fig 1b). Among patients with relapse in rituximab arm, the efficacy of a second infusion of rituximab, infused in accordance with the protocol, was not affected by the presence of anti-rituximab antibodies (Fig 1c).

Conclusions: Previous exposure to rituximab results in production of anti-CD20 antibodies, which persist for a limited time. Presence of circulating anti-rituximab antibodies does not affect response to rituximab in steroid dependent nephrotic syndrome.

SA-OR34
Glomerular Exostosin as a New Subtype and Activity Marker for Membranous Lupus Nephritis
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Background: Exostosin (EXT) expression has been shown to be related to membranous lupus nephritis (MLN). This study analyzed the distribution of EXT in MLN and its correlation with the activity, histological transformation and progression of MLN.

Methods: The renal biopsy specimens from MLN, other types of lupus nephritis (LN), other disease-related membranous nephropathy (MN), and PLAR-related MN were included. EXT expression was detected by immunohistochemistry and was quantitatively determined by computer image analysis. The correlations between proteinuria and EXT expression, the differences between EXT-positive and EXT-negative MLN, and the relationship between pathological changes and EXT expression were analyzed by repeated renal biopsy.

Results: Of the 153 MLN, 47.7% were EXT positive; of the other types of LN, only 6.8% were EXT positive. The EXT-positive rates for Hashimoto’s thyroiditis, Sjogren and HBV related MN were 16.7%, 10.0% and 10.0%, respectively; EXT was negative in psoriasis, mercury poisoning, tumor and GVHD or the PLA2R related MN. The EXT-positive rates in groups with 24-h urinary protein of <1 g, 1-2.29 g, 3.0g-4.9 g and ≥5.0 g were 32.3%, 39.6%, 50.0% and 68.4%, respectively (P<0.013), and EXT expression intensity was also positively correlated with proteinuria (r=0.78, P<0.001). When the EXT-positive was compared with the EXT-negative MLN, 24h urinary protein (P<0.001) and the proportion of massive subepithelial immune deposits (P<0.001) were higher, and the serum albumin (P<0.001), and CI (P<0.05) and renal tubular atrophy score (P<0.05) were lower. There were no significant differences in renal survival between the two groups. A total of 47 MLN (18 EXT-positive and 29 EXT-negative) underwent repeat renal biopsy after treatment or recurrence. For EXT-negative MLN, EXT remained negative in repeated biopsy regardless of pathological type (class V or class V/III/IV after transformation); for EXT-positive MLN, EXT became negative or EXT expression was reduced after renal remission, and as shown in repeated biopsy after recurrence: 62.5% of MLN without histological transformation were still EXT positive, but 80% of cases whose histological class became class V with III or IV were EXT negative.

Conclusions: Our study indicated that EXT expression in MLN could be used as a marker of diagnosis and activity, and a histological subtype marker of MLN.

SA-OR35
Computationally Extracted Peritubular Capillary Shapely Is Associated with Progression in Glomerular Diseases
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Background: In CKD models, the association between peritubular capillary (PTC) density and outcome has been demonstrated, but little is known about PTC pathologic features in glomerular diseases. We explored whether computer extracted features quantifying PTC shape and density can predict risk of progression (40% eGFR decline or kidney failure) in proteinuric diseases.

Methods: N=388 PAS-stained whole slide images from the NEPTUNE database were included: 133 Focal Segmental Glomerulosclerosis (FSGS), 55 IgA Nephropathy (IgAN), 109 Minimal Change Disease (MCD), and 61 Membranous Nephropathy (MN). The presence of segmental sclerosis (SS) further subclassified IgAN and MN. The kidney cortex was manually annotated, and a pre-trained deep learning model generated PTC segmentations (Fig 1). Average PTC flatness (the PTC major and minor axis ratio) and cortical density (PTC pixels/unit cortical area) were digitally measured. Unadjusted Cox proportional hazards models were used to associate normalized PTC flatness and density with outcome across and within each disease, within cases with SS (FSGS, IgAN+SS, MCD+SS), and cases w/o SS (MN w/o SS), and with gender and age. Results: PTC flatness at0.469 significantly associated with a hazard ratio (95% CI) of progression of 1.99 (1.19-3.33) compared with normalized PTC flatness <0.469 (p=0.0109) (Fig 1). PTC cortical density at0.135 associated with a hazard ratio (95% CI) of progression of 0.689 (0.398 – 1.19) compared with normalized PTC cortical density >0.135 (p=0.16). PTC flatness significantly associated with outcome in FSGS (p<0.045), in the presence of SS (p=0.022), in males (p=0.0138), and adults (p=0.016), but not in children, females, or patients w/o SS.

Conclusions: PTC flatness was significantly associated with progression in glomerular diseases, particularly in patients with SS. This association is age and gender dependent.

Funding: Private Foundation Support

Figure 1
SA-OR36

Abstract Withdrawn

SA-OR37

Upregulated JAK-STAT Signaling and Augmented Potassium Efflux Characterize Induced Pluripotent Stem Cell-Derived Podocytes of Black Patients with APOL1-Associated FSGS

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Background: High risk (HR) APOL1 genotypes account for 70% of excess risk of FSGS among Blacks. It is unknown why ~20% of carriers of HR APOL1 genotypes develop FSGS or other APOL1 nephropathies while 80% kidney disease-free. The possible role of genetic modifiers has been proposed. Also, the mechanism by which variants APOL1 cause podocyte injury is unknown. We previously reported that overexpression of variants APOL1 in HEK293 cells caused cytotoxic loss of cellular K+. It is unknown if physiologic expression of APOL1 by IFN also causes K+ loss in patient-derived podocytes.

Methods: We recruited Blacks with biopsy-proven FSGS (n=16) or with normal GFR and no proteinuria (n=20). 68.7% and 10% of FSGS cases and healthy controls carried APOL1 HR APOL1 genotypes, respectively. Markers-confirmed iPSC-podocytes generated from patient-derived podocytes.

Results: Notably, the 520 differentially expressed genes (DEGs) unique to HR cases are transcriptionally regulated by JAK-STAT signaling (Fig. A-B). Consistent with this finding, IFNγ induces a higher expression of APOL1 in HR cases which was blocked by JAK1/2-specific inhibitor, Baricitinib (Fig. C). Importantly, for the first time, we demonstrated that physiologic expression of variant APOL1 under its endogenous promoter causes significant loss of cellular K+ in iPSC-podocyte of HR cases and was abolished by APOL1-knockout (Fig D-E).

Conclusions: JAK-STAT signaling may be an important modifier of APOL1-associated FSGS that upregulates APOL1 expression and function (K+ efflux). Inhibition of JAK-STAT signaling and/or blockade of APOL1-mediated cation-transport may represent targeted therapeutic approach for APOL1-associated FSGS.

Funding: Other NIH Support - Common Fund (NIH Director’s New Innovator Award)

SA-OR38

Transcriptional Reprogramming by Wilms’ Tumor 1 and FoxC2 Mediates a Repair Response During Podocyte Injury

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Background: We previously demonstrated a transcriptional response to injury in podocytes and identified WT1 as one of the most upstream transcription factors binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. We now demonstrate that FoxC2 transcription factor is a major component of the response to injury, binding many of the same genes as WT1. Here, we focus on understanding WT1 and FoxC2 transcriptional mechanism in response to injury.

Methods: We used Adriamycin (ADR)-induced podocyte injury as a model for human Focal Segmental Glomerulosclerosis in mice and performed FoxC2 ChIP-seq from isolated podocytes. WT1 is required for the podocyte response to injury. Conditional WT1 knockout and FoxC2 knockout mouse models were used to decipher the transcriptional mechanism through which WT1 and FoxC2 regulate podocyte gene expression during injury, using transcriptomic approaches.

Results: WT1 is required for the podocyte response to injury. Indeed, the transient increased expression of podocytes genes in mice after injury, was abolished in the absence of WT1. We found that FoxC2 was also actively involved during this response. By ChIP-seq, we detect 4214 FoxC2 binding sites before injury, rising to 12,532 after ADR. In contrast to WT1, that maintains a moderate degree of binding during the later stages of injury, FoxC2 binding is essentially absent. Using a set of 48 podocyte genes encoding components of the glomerular filtration barrier, ChIP-seq analyses demonstrated that WT1 and FoxC2 both acquire novel binding sites during the early stages of injury. One co-bound site is at the WT1 transcriptional start site, where binding of both WT1 and FoxC2 increases dramatically after injury. Furthermore, WT1 and FoxC2 may be co-immunoprecipitated and knockdown of WT1 or FoxC2 in immortalized podocytes demonstrated their mutual dependence for binding target genes.

Conclusions: Together, these results demonstrate that WT1 and FoxC2 mediate transcriptional reprogramming during podocyte injury. This transcriptional reprogramming may be initiated by the dramatic increased binding of WT1 and FoxC2 at the WT1 transcriptional start site after injury. Irreversible podocyte injury leading to FSGS may result from the nearly complete loss of FoxC2 binding to target genes during later stages of injury.

Funding: NIDDK Support

SA-OR39

Cytosolic Phospholipase A2: A Drug Target in FSGS

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common glomerular cause of end stage kidney disease (ESKD) in children. The refractory nature of FSGS renders treatment of FSGS as one of the most difficult challenges in pediatric nephrology. A significant knowledge gap in understanding the mechanism of progression in FSGS hampers development of successful treatment strategies. We demonstrated that patients with FSGS present with a distinct urinary lipid profile characterized by increased fatty acids (FA) and lysophosphatidylcholines (LPC), metabolites of cytosolic phospholipase A2 (cPLA2). We propose that LPC and FA incites proinflammatory and proapoptotic response in podocytes and proximal tubule epithelial cells (PTECs). We hypothesize that increased cPLA2 activity induces apoptosis, fibrosis and progression in FSGS by harboring intracellular LPC and FA.
**Methods:** A bigenic model of FSGS was induced by mutation of Fyn and Cd2ap (Fyn/Cd2ap). A second model was generated by injecting scFv cPLA2-tertiary antibodies into kidney capsules of mice. Animals subjected to adriamycin were treated by intraperitoneal cPLA2 inhibitor (AAOCOCF3-4mM) versus saline for 6 weeks. Untargeted lipodomics was performed in urine and kidney lysates of FSGS mice by CSH-QTOF MS/MS. cPLA2 expression in podocytes and PTECs was investigated by RNA sequencing. Western blotting and immunofluorescence staining was utilized to examine C-terminal cPLA2 expression.

**Results:** Lipid profiling revealed increased urinary LPC and FA and increased LPC levels in kidney lysates of FSGS mice reminiscent of human data. FSGS mice kidneys displayed increased cPLA2 activity in podocytes and PTECs. RNA seq data revealed upregulation of cPLA2 in podocytes and PTECs in FSGS mice. Treatment with AAOCOCF3 decreased proteinuria and ameliorated kidney dysfunction, FSGS pathology and tubulointerstitial fibrosis.

**Conclusions:** Our data strongly suggest that increased C-terminal cPLA2 expression contributes to progression of FSGS by harboring production of proinflammatory and propropagated lipid metabolites. We propose that upregulated C-terminal cPLA2 activity leads to podocytes and PTEC damage by perpetuating oxidative injury, apoptosis, inflammation and subsequent fibrosis in FSGS. We postulate that targeting cPLA2 pathway for drug development will improve kidney function and basal monotherapy in FSGS.

**Funding:** Commercial Support - Kaneka

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**SA-OR42**

**Elevated Load with Normal Mean in Pediatric Hypertension (HTN): What Does It Mean?**

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**Background:** Current pediatric ambulatory blood pressure monitor (ABPM) guidelines define HTN as mean blood pressure (BP) ≥ 95th percentile for gender and age/height. For children >12 years, those with a normal mean BP but elevated load are considered “unclassified.” Adult ABPM criteria is based solely on mean BP using an absolute threshold. Applying pediatric versus adult ABPM criteria in adolescents has been a topic of research recently as the 2017 pediatric BP guidelines use adult norms to define clinic HTN in patients (pts) ≥ 13 years (yrs). However, research on the utility of BP load in defining pediatric HTN is limited. We aimed to evaluate the significance of elevated BP load in “unclassified” pts by ABPM including association with left ventricular hypertrophy (LVH).

**Methods:** Retrospectively, pts 13-17 yrs with ABPM data between 9/2018 and 7/2019 were categorized by pediatric ABPM guidelines using only ABPM data. Data collected included gender, age, height, ABPM systolic and diastolic BP mean and load ≥ 25%. LVMI was defined as LVMI > 51 g/m². Results: 495 pts (35.5 M) had ABPM. 146 had HTN; 198 (121 M) were “unclassified.” 52 pts with normal BP and 101 of unclassified pts had LVMI data. There was no significant difference in mean LVMI in pts with “unclassified” versus normal BP (41 ± 40 g/m² vs 40 ± 40 g/m² p=0.23). Pts re-cat to HTN by adult criteria, and there was no difference in LVMI compared to pts re-class to normal BP (40.6 ± 37.4 g/m² vs 42.6 ± 39.4 g/m² p=0.23). Pts re-cat to HTN, had significantly higher loads for night BP and 24hr systolic BP compared to those with normal BP. However, there was no difference between the mean loads when comparing those with LVH versus those without LVH.

**Conclusions:** For adolescents with a normal mean BP by pediatric criteria, elevated BP loads are not associated with LVH. Furthermore, applying adult criteria to define pediatric HTN would appropriately classify those with higher loads. Regardless of later re-classification, there is still no difference in LVMI. Applying adult BPABM standards for adolescents would simplify interpretation without sacrificing significance.
criteria: two eGFR<90 mL/min/1.73m² separated by ≥1 days without an intervening higher value. CKD progression was defined as composite outcome: eGFR<15 mL/min/1.73m², 50% eGFR decline, chronic dialysis, or kidney transplant. Subcohorts were based on CKD etiology: glomerular, non-glomerular or malignancy. We assessed impact of hypertension(HTN) (≥2 visits with HTN code) and proteinuria (a1 lab value ≥a1+) within 2yrs of cohort entrance on outcomes.

Results: We identified 7395 children, median age 14.1yrs, 36% females, 23% blacks, median follow-up 4.2yrs. Median initial eGFR was 75.5 mL/min/1.73m²; 36% had proteinuria; 46% had HTN. Children with glomerular CKD were more likely to reach outcomes (p<0.001). Children with HTN, proteinuria, or both were more likely to reach outcomes (p<0.001).

Conclusions: The EHR may be used to study large numbers of children with CKD. Risk factors for CKD progression were glomerular disease, HTN and proteinuria.

Funding: Other U.S. Government Support, Commercial Support - Institute for Advanced Clinical Trials for Children, Bayer.

Endpoint reached by sub-cohort

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Noe-CKD (%)</th>
<th>Glomerulopathy (%)</th>
<th>Malignancy (%)</th>
<th>Oral (854)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td>364 (14.7%)</td>
<td>491 (18.6%)</td>
<td>374 (27.3%)</td>
<td>1,459 (51.5%)</td>
</tr>
<tr>
<td>eGFR&lt;60</td>
<td>273 (12.7%)</td>
<td>474 (18.4%)</td>
<td>412 (31.9%)</td>
<td>1,397 (47.7%)</td>
</tr>
<tr>
<td>eGFR&lt;15</td>
<td>354 (6.9%)</td>
<td>351 (12.9%)</td>
<td>91 (6.1%)</td>
<td>504 (17.9%)</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>395 (9.8%)</td>
<td>172 (14.1%)</td>
<td>23 (1.9%)</td>
<td>372 (4.8%)</td>
</tr>
<tr>
<td>Chronic diabetes</td>
<td>641 (14.6%)</td>
<td>90 (6.2%)</td>
<td>15 (1.2%)</td>
<td>180 (13.3%)</td>
</tr>
</tbody>
</table>

SA-OR44

Risk Factors for Kidney Injury in Children with Solitary Functioning Kidney

Sander Groen in’t Woud, Nel Roolsveld, Wout Feitz, Michiel F. Schreuder, Loes F. van der Zanden. SOFIA study group Radboudumc, Nijmegen, Netherlands.

Background: Patients with a solitary functioning kidney (SFK) are at increased risk of kidney injury, for which several risk factors have been suggested. Large differences exist between previously reported cohorts, which hampers translation of these findings into clinical care. Our objective was to investigate the risk of and risk factors for proteinuria, high blood pressure, a decreased glomerular filtration rate (GFR), or use of antihypertensive medication in our nationwide study of children with SFK.

Methods: Children with congenital and acquired SFK were recruited in >30 hospitals into clinical care. Our objective was to investigate the risk of kidney injury. Other risk factors will be investigated in our cohort to develop care strategies based on individual-patient risk profiles.

Results: Of 982 patients who provided informed consent, detailed clinical information was available from 898 (91%). Of 921,229 neonates, 74% were treated with at least one NM, Figure 1. AKI prevalence was significantly higher in the NM group (aRR 3.68 [95% CI: 2.85, 4.75]), Figure 2. The aRRs of treatment were increased in <32-week, and <2000 g infants. NMs were prescribed to 90-95% of ≤32-week gestational age (GA) neonates. Most treatments with NM (95-98%) occurred in the first 3 postnatal days. IV aminoglycosides were the most frequent NM prescribed; 28% were treated with a 4 calendar days. Most common diagnoses were infections (25%) and patent ductus arteriosus (20%).

Conclusions: The smallest and most immature preterm neonates are frequently treated with NM. The prevalence of AKI is higher in the NM treated group. The long-term implications of treatment with NM and subsequent AKI on nephrogenesis warrant attention in future studies.

SA-OR45

Nephrotoxic Medications and Associated AKI in Hospitalized Neonates

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Background: Hospitalized neonates in the NICU are frequently treated with nephrotoxic medications (NM), a risk factor for acute kidney injury (AKI) which is associated with increased neonatal morbidity and mortality. Neonatal treatment with NM and subsequent AKI, especially in pereivable neonates could be detrimental to nephrogenesis.

Methods: Multicenter retrospective analysis of hospital discharges (2005-2016) using the national Pediatric Hospital Information System database, including 49 pediatric hospitals across the U.S. Treatment with 37 NM in first 28 postnatal days across demographics and clinical variables, and relationship with AKI were evaluated.

Results: Of 192,229 neonates, 74% were treated with at least one NM, Figure 1. AKI prevalence was significantly higher in the NM group (aRR 3.68 [95% CI: 2.85, 4.75]), Figure 2. The aRRs of treatment were increased in <32-week, and <2000 g infants. NMs were prescribed to 90-95% of ≤32-week gestational age (GA) neonates. Most treatments with NM (95-98%) occurred in the first 3 postnatal days. IV aminoglycosides were the most frequent NM prescribed; 28% were treated with a 4 calendar days. Most common diagnoses were infections (25%) and patent ductus arteriosus (20%).

Conclusions: The smallest and most immature preterm neonates are frequently treated with NM. The prevalence of AKI is higher in the NM treated group. The long-term implications of treatment with NM and subsequent AKI on nephrogenesis warrant attention in future studies.
SA-OR46

Urinary VEGF as a Prognostic Biomarker of CKD in Premature Infants with Lung Disease

Michelle C. Starr,1,2 Brian A. Halloran,3 Robert Schmicker,4 Patrick D. Brophy,5 Patrick J. Heagerty,6 Sandra Juul,3 Stuart Goldstein,5 Sangeeta R. Hingorani,7 David J. Askenazi.5 Preterm Erythropoietin Neuroprotection Trial Investigators

Background: Premature neonates are at risk for chronic kidney disease (CKD). Lung disease is an emerging risk factor for CKD in infants. Impaired angiogenesis may be implicated as it is required for both lung and kidney development, repair from injury, and perturbations contribute to CKD development. VEGF is a marker of angiogenesis. We hypothesize that urinary VEGF would be lower in infants with lung disease who go on to developed CKD.

Methods: Using data from the REPAIReD study (NCT01378273) an ancillary of the PENUMUT trial, we assessed urinary VEGF in 40 infants with severe lung disease defined by respiratory support or supplemental oxygen at 36 weeks post-menstrual age (PMA). We measured urinary VEGF at 30-34 weeks PMA. Our outcome measure was CKD at 22-26 months (estimated glomerular filtration rate <90 ml/min/1.73m²). Urinary VEGF was determined with electro-chemiluminescent multi-analyte ELISA (Mesoscale). We compared values using Spairo-Wilk testing and ROC analysis with Youden’s index.

Results: Fourteen infants (35%) developed CKD. Urinary VEGF at 30-34 weeks PMA was lower in infants that developed CKD (2.23 ± 2.63 log pg/mL; p=0.004). The AUC for VEGF to predict CKD was 0.77 (95% CI 0.62-0.92, p=0.005). Using a likelihood ratio of 2.32, a threshold of 2.47 log pg/mL gives a sensitivity of 72% and specificity of 70% (Figure 1).

Conclusions: In this small cohort of premature infants with severe lung disease, urinary VEGF levels were lower in premature infants who went on to developed CKD compared to similar neonates who did not develop CKD. Additional urinary VEGF analysis in this cohort is ongoing. Low urinary VEGF may be a marker of abnormal angiogenesis and vascular repair in the kidney. Our findings suggest that urinary VEGF may help predict CKD in premature infants with lung disease.

Funding: NIDDK Support

SA-OR47

Hyperoxia Exposure in Neonatal Period Is Associated with Decrease in HB-EGF Expression in Mice Kidneys

Rishika P. Sakaria,1 Catrina White,1 Ahmed Abdelgawad,2 Ajay J. Talati,2 Kent A. Willis,3 Amaneep Bajwa.1 The University of Tennessee Health Science Center, Memphis, TN; 2The University of Alabama at Birmingham School of Medicine, Birmingham, AL

Background: Acute Kidney Injury (AKI) is common in preterm infants and may cause lasting renal damage. Hyperoxia-exposure in the postnatal period has been linked to chronic kidney disease (CKD) in adulthood in survivors or preterm birth. The mechanism of hyperoxia-driven AKI in premature infants is not clearly understood. Activation of the epidermal growth factor receptor (EGFR) by EGF or heparin-binding EGF-like growth factor (HB-EGF) promote renal tubular proliferation and renal recovery in AKI. In contrast, activation of transcribing growth factor (TFG-a) signaling may lead to fibrosis and CKD. We hypothesize that hyperoxia exposure in neonatal mice leads to kidney injury via alteration in the expression of EGFR and its ligands.

Methods: Pups of C57Bl/6J mice were exposed to hyperoxia (FiO2 0.85) and compared to littermate controls exposed to room air from postnatal days 3-10. One kidney from each pup was fixed in formalin and embedded in paraffin for histological analysis. The other kidney was snap frozen and RT-PCR was performed from the RNA isolated from each pup was fixed in formalin and embedded in paraffin for histological analysis.

Results: We analyzed renal tissues from 15 newborn mice (from 3 litters) exposed to hyperoxia and 5 mice (from 1 litter) exposed to normoxia. Relative mRNA levels of HB-EGF were significantly decreased in renal tissues of pups exposed to hyperoxia (mean±0.006 ± 0.001) compared to those exposed to normoxia (mean±0.012 ± 0.002) (p < 0.05). Both EGRF and TGF-α were not elevated in pups exposed to hyperoxia. Hyperoxia-exposed pups were also noted to have elevated a-SMA and fibronectin compared to the controls. TGF-β levels were also similar between exposed and non-exposed animals (Figure 1).

Conclusions: HB-EGF may contribute to hyperoxia-related renal injury in preterm neonates and may be a therapeutic target in these infants.

Funding: Other NIH Support - NIH, NHLBI K08 HL151907

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

SA-OR48

Identification of Molecular Mechanisms Regulating Mammalian Nephrogenesis Duration and Nephron Endowment

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Background: Nephron endowment generated during development confers lifelong renal filtration function, and is established via nephron progenitor cell (NPC) interactions with the adjacent stroma and ureteric bud (UB). Two salient, incompletely understood features of nephrogenesis are (1) the coordinated cessation of nephrogenesis in independent niches and (2) a striking 10-fold variation in nephron number between kidneys from different individuals. Preterm births are associated with premature cessation of nephrogenesis and are consequently susceptible to early-onset chronic kidney disease (CKD) and end-stage renal disease (ESRD). We leverage multiple mouse models exhibiting consistent differences in nephron number to identify mechanisms promoting prolonged nephrogenesis and/or increased nephron endowment.

Methods: NPCs from mice with elevated nephron numbers and delayed cessation (Six2TG+; Tsc1-/-) were evaluated via single-cell transcriptomics, translatome profiling (bulk RNA-Seq of Rp110-associate transcripts), metabolic indicators (in vitro glycolysis assays and in vivo hyperoxia studies), and immunofluorescence. Candidate genes emerging from the RNA analyses were validated in in vivo genetic models for nephron number and cessation timing phenotypes.

Results: Translatome analysis revealed age and genotype-dependent patterns in signaling pathway components that were not observed in the single cell transcriptome, including differential translation of Wnt antagonists over agonists (such as R-spondin-3) in Tsc1-/- NPCs. Moreover, compared to postnatal day 0 nephrons, Wnt agonists are less robustly translated in younger (embryonic day 14) nephrons, reaching high Egr20 levels and high R-spondin levels promoting a self-renewal environment. Further, the selective differential translation observed in the Tsc1-/- model was not associated with globally elevated mTORC1 activity or changes in cellular metabolic activities.

Conclusions: We propose a model in which the tipping point for nephron progenitor exit from the niche is controlled by the gradual increase in stability of Wnt/Fzd complexes—such as structural maintenance, hemodynamics, and kidney endocrine function—must be generated. Previously, we successfully generated a rat nephron using mouse kidney as a scaffold by replacing mouse nephron progenitor cells (NPCs) with rat NPCs. Therefore,

SA-OR49

Simultaneous Generation of Nephron and Renal Stromata via Progenitor Cell Replacement in Animal Fetus

Yatsumu Saito, Shuichiro Yamakata, Kenji Matsui, Naoto Matsumoto, Tatsushi Takamura, Toshinari Fujimoto, Susumu Tajiiri, Kei Matsumoto, Eiji Kobayashi, Takashi Yokono. Tokyo Jikeikai Bia Daigaku, Tokyo, Japan.

Background: To solve the organ transplant shortage by regenerative medicine, the whole kidney, including the renal stroma—which plays important roles in homeostasis, such as structural maintenance, hemodynamics, and kidney endocrine function—must be generated. Previously, we successfully generated a rat nephron using mouse kidney as a scaffold by replacing mouse nephron progenitor cells (NPCs) with rat NPCs. Therefore,
animal fetuses can potentially generate human kidneys. Herein, we applied progenitor cell sorting to mNPCs and mSPCs to verify the simultaneous generation of renal stroma and nephrons.

Methods: We harvested the metanephroi of green fluorescent protein rats to extract dissociated single cells (DSCs) by enzymatic treatment. SPCs were extracted from the DSCs by cell sorting targeting the platelet-derived growth factor receptor alpha (PDGFRα)-positive fraction. NPCCs were extracted by selecting integrin alpha 8-positive fractions from the PDGFRα-negative fraction. We injected the extracted SPC fractions and both NPC and SPC fractions in the nephrogenic zone of the metanephros of Foxd1- /DTR mice (host SPC removal model) and Six2/Foxd1-DTR mice (host NPC removal model), respectively. The metanephroi were organ cultured for 1 week or transplanted into the retroperitoneum of NOD/Shi-scid/IL-2Rγnull mice and collected after 2 weeks for evaluation with immunofluorescence staining.

Results: In the in vitro model, mNPCCs were replaced with rat SPCs in vitro, and rat stroma was extensively generated in mouse kidneys in vivo. Rat SPCs differentiated into various stromal lineage cells, e.g., mesangial cells, interstitial fibroblasts, vascular pericytes, juxtaglomerular cells, and EPO-producing cells. In the two progenitor cell removal models, cap mesenchyme-like structures were formed with aggregated rat NPCs and SPCs around the mouse ureteric bud in vitro. Rat nephrons and renal stroma were generated in the mouse kidney in vivo.

Conclusions: SPC replacement helped generate heterogeneous rat renal stromal lineage cells in the mouse kidney. Simultaneous NPC and SPC replacement enabled the generation of nephrons and renal stroma between different species.

SA-OR50
Crescents Derive from Single Podocyte Progenitors and a Drug Enhancing Their Differentiation Attenuates Rapidly Progressive Glomerulonephritis
Maria Elena Melica, Giulia Antonelli, Maria Lucia Angelotti, Giannareg Morgali, Carolina Conte, Letizia De Chiara, Fiammetta Ravaglia, Anna J. Peired, Benedetta Mazzinghi, Elena LaZzeri, Roberto Semeraro, Laura Lasagni, Paola Romagnani. Università degli Studi di Firenze, Firenze, Italy.

Background: Rapidly progressive glomerulonephritis (RPGN) is characterized by crescent formation, which typically, is the consequence of diverse upstream pathomechanisms involving the specific activation of PEC, represents which present in part renal progenitor cells (RPC). Similarities with stem cell of bone marrow prompted us to hypothesized that crescents result from clonal expansion of a single RPC, conceptually similar to monoclonal diseases originating from hematopoietic stem cells. We further hypothesized that drugs known to cure hematopoietic disease by enforcing their terminal differentiation could also attenuate crescentic glomerulonephritis.

Methods: We established a RPGN disease model in a conditional transgenic mouse based on the mT/mG and the Confetti reporter that allows lineage tracing of RPC. Mice were treated with drugs currently used in myeloproliferative disorders. Crescentic lesions were characterized by super-resolution STED microscopy. Single cell RNA sequencing of human renal progenitor cultures identify the immature progenitor subset generating crescent in human.

Results: We observed that crescents originated from the clonal expansion of single RPC, thus suggesting a clonal stem cell disorder. Therefore, we administrated a series of drugs known to ameliorates myeloproliferative neoplasms to our mouse model. Treatment with one of the compounds induced a reduction in both proteinuria and crescent formation. 3D confocal microscopy and STED super-resolution imaging of glomerular showed that this compound turned the uncontrolled hyperplasia of an immature PEC subset into a controlled differentiation into new podocytes restoring the injured glomerular filtration barrier. Single cell RNA of human renal progenitor cultures identified a new marker of the crescent-generating progenitor cells. Expression of this marker in biopsies of patients with RPGN associated with progression toward end stage kidney disease.

Conclusions: These results demonstrate that glomerular hyperplastic lesions derive from clonal amplification of a RPC subset and that shifting proliferation to podocyte differentiation reverses crescent formation and improves clinical outcome.

SA-OR51
A Multimodal Single Cell and Spatial Atlas of the Human Kidney in Health and Disease Delineates Cell States Associated with CKD
Santosha Jain,1 Blue Lake,2 Rajasree Menon,3 Seth Winfree,2 Qiwen Hu,3 Ricardo Mello Ferreira,4 Edgar A. Otto,1 Darwina Barinska,1 Kim Kalbow,2 Michael J. Ferkovich,4 Abhijit S. Naik,4 Evan Murray,3 Sean Eddy,3 James C. Williams,2 Karol S. Balderrama,1 Chirag R. Parikh,1 Eric H. Kim,1 Peter Kharchenko,4 Joseph Gaut,1 Jeffrey B. Hodgkin,4 Michael T. Eadon,3 Pierre C. Dagher,3 Tarek M. El-Achkar,2 Kun Zhang,2 Matthias Kretzler,3 KPMP, HubMAP 3Washington University in St Louis, St Louis, MO; 1University of California System, San Diego, CA; 3Harvard Medical School, Boston, MA; 4Indiana University School of Medicine, Indianapolis, IN; 1University of Michigan Michigan Medicine, Ann Arbor, MI; 2Broad Institute, Cambridge, MA; 3Johns Hopkins University, Baltimore, MD.

Background: The knowledge of the complexity of cell types, states and their interactions during homeostasis or disease is needed to identify the mechanisms of kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Methods: We have applied multiple single cell or nucleus omic assays (~400,000 nuclei/cells) that capture gene regulation, expression and their spatial relationships to a broad spectrum of healthy reference (35) and disease kidney tissues (50, AKI or CKD) to establish a robust atlas of the cellular diversity representing kidney function or dysfunction.

Results: We identified 100 cell clusters including rare and novel cell populations and their spatial locations spanning the entire kidney. Among these, we define cellular states associated with kidney injury alterations that represent cycling, adaptive or maladaptive repair and degenerative states, their associated regulatory factors, and genes and pathways underlying these transitions. Molecular signatures of those states permit their classification and spatial localization within injury neighborhoods, allowing discovery of intercellular signaling relevant to acute or chronic injury. Large scale 3D imaging linked glomerular, proximal tubule and thck ascending limb injured cells to an active immune barrier that is uniquely associated with tubular cells. The altered state gene signatures were negatively associated with a decline in eGFR in patients with chronic kidney disease in two separate cohorts.

Conclusions: This comprehensive molecular, cellular and spatial atlas serves as a benchmark to identify nascent and altered kidney cell states, define therapeutic targets in individual patient samples and engineer healthy kidneys.

Funding: NIDDK Support, Other NIH Support - Common Fund (NIHBI)
SA-OR53
Proteomic Characterisation of CKD Progression
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Background: Delaying or halting progression of chronic kidney disease (CKD) to established renal failure is a major goal of global health research. The mechanism of CKD progression among different CKD entities involves pro-inflammatory, pro-fibrotic, and pro-angiogenic vascular pathways but current treatments are non-specific, with heterogeneity in terms of response and outcome. In depth phenotypic and proteomic data can help investigate differences between those CKD patients with rapid disease progression and those who remain stable after diagnosis.

Methods: Using eGFR slope analysis, 414 patients with a broad range of kidney disease aetiologies were divided into fast progressors (ΔGFR > -3 ml/min/yr; n=170) and stable patients (ΔGFR > 0 ml/min/yr; n=244); these composed our discovery cohort. Plasma samples were collected and interrogated for protein signals with SWATH-MS which enabled a digitised proteomic profile to be generated. For hypothesis testing, the t-test was used to identify differentially expressed proteins between our patient groups (p<0.05, after multiple testing corrections was considered statistically significant). Statistical analysis and machine learning approaches for discovery (Random Forest and Boruta Feature Selection) were performed using the computing environment R and additional software packages were obtained via the Bioconductor project.

Results: A SWATH map (on 414 patients with 943 proteins quantified) was generated and further filtered with available clinical data in order to identify potential progression biomarkers. After differential expression analysis and supervised machine learning algorithms for feature selection, we identified a set of proteins that differentiate between our patient groups (AUC= 0.77). Baseline creatinine was not an accurate predictor of CKD progression (AUC=0.51). Functional enrichment analysis revealed platelet degranulation to be statistically important, suggesting a possible role for platelet function in then pathogenesis of CKD.

Conclusions: The in-depth proteomic characterisation of this large-scale CKD cohort using state-of-the-art technology and machine learning tools that might lend themselves to future drug targeting. Candidate proteomic biomarkers will be validated in samples from selected patients in other large CKD cohorts such as NURTuRE using a cohort is a step forward in generating mechanism based hypotheses that might then lend themselves to future drug targeting. Candidate proteomic biomarkers will be validated in samples from selected patients in other large CKD cohorts such as NURTuRE using a targeted mass spectrometric analysis.

SA-OR54
Capillaries Are Primary Targets in CKD and Tie2 Signaling Plays a Central Role in Disease Progression
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Background: Progressive renal diseases are associated with loss of peritubular capillaries, capillary rarefaction, but the underlying mechanisms are not well described. In both mouse models and patients, a decline in endothelial tyrosine kinase receptor (Tie2) signaling can be seen in CKD. We hypothesized that renal blood vessels through loss of Tie2 signaling upregulates Pdgfb that in turn act as a mitogen to activate pericytes and fibroblasts.

Methods: To investigate this, we utilized floxed alleles for Tie2 and Pdgfb together with inducible endothelial specific Cre and lineage reporter. Additional lines (Pdgfra-H2b-GFP and Pdgfb-GFP), were crossed into the line, resulting in reporters of myofibroblasts. Mice were subjected to an experimental model of CKD, the unilateral ureter obstruction model. Capillary density and fibrosis were evaluated at 1, 3, and 10 days after obstruction. A subset of mice was treated with an Tie2 activating antibody and evaluated the same way.

Results: Our studies show that loss of Tie2 results in increased injury to peritubular capillaries and increased tubulointerstitial fibrosis in an experimental model of CKD. Tie2 cKO mice showed reduced capillary density, reduced renal fibrosis, and reduced vasa recta perfusion. Furthermore, treatment with an Tie2 activating antibody reduced both fibrosis and loss of capillaries if started at the time of injury, while endothelial specific knockout of Pdgfb only reduced fibrosis.

Conclusions: Our results suggest that capillaries are primary targets in CKD and that Tie2 regulation affects both capillary density and tubulointerstitial fibrosis. Tie2 activating agents should be explored as therapies for patients with chronic kidney disease.

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SA-OR55
Autocrine Signaling of Sphingosine 1 Phosphate in Kidney Pivotal Cell Functions Promotes Inflammation and Fibrosis
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Background: Sphingosine 1-phosphate (S1P) is a sphingolipid that is produced inside the cell by the action of sphingosine kinase (Sphk) 1 and 2. S1P is exported from cells by spinster homolog 2 (Spns2) or major facilitator superfamily 2b (Mfsd2b), and then acts on five G protein-coupled S1P receptors, S1P1 to S1P5, to affect various cellular functions. We recently showed that Sphk2+/- mice were protected from renal fibrosis when compared to wild type or Sphk1+/- mice (PNAS: 13885). We hypothesized that local S1P signaling in kidney perivascular cells affects the progression of kidney fibrosis.

Methods: Male Foxd1Cre+ Sphk2+/+, Foxd1Cre+ Sphk2+/-, Foxd1Cre+ Spns2+/-, and their littermate control mice were used. For unilateral ischemia-reperfusion injury (IRI), left kidneys were clamped, right nephrectomy was performed at day 13. In the folic acid model, folic acid (250 mg/kg) was intraperitoneally injected. Mice were euthanized at day 14 to evaluate kidney fibrosis. Primary kidney perivascular cells were isolated from kidneys and used for in vitro studies.

Results: Both in the unilateral IRI and folic acid models, Foxd1Cre+ Sphk2+/+ and Foxd1Cre+ Spns2+/- mice demonstrated better kidney function (plasma creatinine/blood urea nitrogen), less kidney fibrosis (histology) with less macrophage infiltration, and suppressed expression of fibrosis-related genes (Acta2, Colla1, Col3a1) in the kidneys compared to controls. In in vitro studies, perivascular cells with Sphk2 deficiency or Spns2fl/fl knockdown expressed less proinflammatory cytokines/chemokines, such as Cc12, Il6, Cxcl1, after treatment with TLR2/4 agonists compared with control cells. We further identified Spns2 as the S1P transporter expressed in kidney perivascular cells. Foxd1Cre+ Spns2+/- mice also showed protection against kidney fibrosis in the unilateral IRI model and Spns2-knockdown cells showed suppressed inflammatory signaling upon stimulation.

Conclusions: SphK2+/S1P/Spns2+/SIP1 axis enhances inflammatory signaling in perivascular cells on injury, which aggravates immune cell infiltration and subsequent fibrosis in the kidney.

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SA-OR56
CD153-CD30 Signaling Is Required for Age-Dependent Tertiary Lymphoid Tissue Expansion in the Kidney
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Background: The elderly show a reduced capacity for renal regeneration after acute kidney injury (AKI). We previously showed that, after AKI, aged, but not young, kidneys exhibit tertiary lymphoid tissues (TLTs), which underlie maladaptive repair in aged injured kidneys. TLTs facilitate lymphocyte activation and differentiation in situ and their expanded roles in pathophysiology in various diseases. However, the cells and signals responsible for age-dependent TLT formation in the kidneys are still undefined.

Methods: We investigated immune cells in aged injured kidneys with TLTs, 45 days after ischemic reperfusion injury, utilizing scRNAseq and bulk RNAseq, combined with flow cytometry and reporter mouse analysis. We also investigated human kidney samples harboring TLTs.

Results: We observed accumulation of CD153+PD1+CD4+ senescent-associated T (SAT) cells and CD30+T-bet+ age-associated B cells (ABCs), within TLTs in aged kidneys. Both SAT cells and ABCs are unique age-dependent lymphocyte populations and have been demonstrated to contribute to the pathophysiology of autoimmune diseases and obesity. By scRNAseq, SAT cells were further divided into two subpopulations, peripheral helper-like T cells and IL10-producing T cells, both of which are specialized CD4+ T cell populations with B cell helper functions. CD153+ and CD30- SAT cells specifically expressed S1P in SAT cells and ABCs, respectively, and their expression was confined within TLTs in aged injured kidneys. In kidney injury models, CD153 or CD30 deficiency reduced ABC numbers, resulting in attenuated TLT formation with less inflammation and more fibrosis. In further renal functional studies, aged SAT cells from TLTs exhibited decreased expression of Il12 and Il10, indicating CD153-CD30 signaling was required for SAT cells to acquire B cell helper functions. CD153-expressing cells were detected within TLTs in human kidneys, and human Tph/Tfh-like cells and ABCs in chronically inflammatory organs also expressed CD153 and CD30, respectively.

Conclusions: These findings identify CD153-CD30 signaling between SAT cells and ABCs as a pivotal regulator of age-dependent TLT formation and suggest that targeting CD153-CD30 signal may be a valuable strategy for the prevention and treatment of kidney diseases in the elderly.

Funding: Government Support - Non-U.S.

SA-OR57
Persistent DNA Damage as a Driver of CKD and Tubular Cell Senescence
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Background: Acute kidney injury (AKI) is a frequent cause of progression to chronic kidney disease (CKD) in humans. Emerging studies have shown that the transition to CKD results from impaired tubular repair due to accumulation of unresolved DNA damage in kidney tubular epithelial cells. Here we identify Fan1, a DNA repair enzyme, as a critical regulator of AKI to CKD progression in response to genotoxic and obstructive kidney injury in mice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.

55
Methods: Gspi-Cre mice were crossed with Fani+/− mice to inactivate FAN1 in kidney proximal tubules. Kidney injury was induced by cisplatin administration (5 weekly injections of 2 mg/kg) or unilateral ureteral obstruction (UUO). Histological analysis was performed using hematoxylin and eosin, periodic acid-Schiff, or Masson’s trichrome staining. Tubular cell senescence was demonstrated by β-galactosidase staining at pH 6.0. Primary kidney proximal tubular cells were used for modeling FANI loss of function in cell culture. RNA-seq analysis was performed on cisplatin-treated FANI-deficient kidneys. Roscovitine was administered to block cell cycle activity and reduce cellular injury in cisplatin-treated FANI kidneys.

Results: Kidney proximal tubule cell-specific FANI inactivation sensitized the kidneys to tubular injury characterized by massive DNA damage response (DDR) activity. We found that persistent DDR triggers tubular cell dedifferentiation, aberrant cell cycle entry and G2 arrest which ultimately led to a failed tubular repair, tubular cell senescence and entry into G2 arrest in FANI kidneys. Transcriptional profiling of FANI kidneys identified that unresolved DNA damage blocks the cell cycle progression in late G2 through p53-dependent p21 upregulation. G2 cell cycle exit in FANI-deficient cells was reinforced by nuclear cyclin D1 accumulation and DNA-replication which gave rise to polyploid karyomegalic cells. Administration of roscovitine effectively blocked cell cycle activity and the formation of karyomegalic cells in cisplatin-treated FANI-deficient kidneys.

Conclusions: Collectively, our data demonstrate that intact DNA damage response (DDR) is critical for proximal tubule regeneration after renal injury, and that FAN1 is a key mechanism whereby CDH11 knockout improves kidney injury. In models of CKD, both genetic and pharmacologic CDH11 inhibition improves renal function (BUN and proteinuria), diminishes cytokine production (TGF-β1 and IL-6 expression), and reduces tubular injury (KIM-1 and histological analysis). RNA-seq from AAN- and Unx/AngII-injured kidneys revealed that CDH11 knockout mice had significantly increased expression of alpha-1 antitypsin (A1AT) compared to wild type controls. Additionally, siRNA knockdown of CDH11 in immortalized PTs in vitro resulted in elevated expression of A1AT, confirming this mechanism in cell culture. The protein inhibitor of A1AT has been used to promote PT survival in several kidney injury models. Using Cox proportional hazards models, we discovered that patients with A1AT mutations have increased incidence of CDK on a per-allele basis, with hazard ratios as high as 5.35.

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SA-OR58
Kidney Tubule Polyploidization Drives CKD Progression After AKI
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Background: Acute Kidney Injury (AKI) is characterized by a rapid rise of kidney injury. In addition, AKI survivors frequently develop chronic kidney disease (CKD). The functional defect of kidney function recovery after AKI is based on a widespread proliferative capacity of injured tubular epithelial cells (TEC), which however is incompatible with the high prevalence of CKD after AKI. We recently demonstrated that TEC respond to AKI not only by proliferation, but also by undergoing polyplodization i.e. increasing DNA content with a time-dependent manner avoids CKD development in comparison to control mice. Interestingly, AKI survivors quickly enter a “window of opportunity” in which they can potentially drive CKD progression.

Results: After AKI, YAPI is activated triggering TEC polyploidization. In YAPI overexpressing mice, a sustained activation of TEC polyploidization after AKI reduces early kidney function recovery, whereas fibrosis is caused by YAPI overexpression. Indeed, healthy YAPI overexpressing mice present a consistent decline of kidney function over time suggesting an association between increased polyploidy and CKD development. Isolation of polyploid cells proves that these cells transcribe pro-fibrotic and senescent factors thus confirming their role in CKD progression. Importantly, polyploid TEC become detrimental over time, blocking YAPI-driven polyploidy in a time-dependent manner avoids CKD development in comparison to control mice.

Conclusions: Collectively, these data suggest that: 1) polyploid TEC are pro-fibrotic leading in the long run to CKD progression; 2) blocking polyploidization in the right window of opportunity, can successfully ameliorate CKD progression after AKI.

SA-OR59
Inhibition of Cadherin-11 Ameliorates Kidney Injury via Restored Expression of Alpha-1 Antitrypsin
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Background: Chronic kidney disease (CKD) represents a massive unmet clinical need, as the pharmaceutical options for treatment of renal injury are extremely limited. A recent study identified cadherin-11 (CDH11) as a potential biomarker for CKD. CDH11 is present in kidney biopsies and urine samples of CKD patients, and its expression is increased in CKD mouse models, but it’s unclear whether it mediates CKD and could be a target for therapy.

Methods: We employed three mouse models of CKD to evaluate the role of CDH11: aristolic acid nephropathy (AAN), unilateral ureteral obstruction (UUO), and uninephrectomy/angiotensin administration (Unx/AngII). In each of these models, we inhibited CDH11 genetically using transgenic mice and pharmacologically with the administration of a functional blocking antibody to CDH11. We also used de-identified electronic medical records (IRB 210049) to verify the clinical relevance of the proposed mechanism whereby CDH11 knockout improves kidney injury.

Results: We found that CDH11 is exclusively expressed in injured murine proximal tubular epithelial cells (TECs) in CKD, as they are both a target and mediator of chronic injury. In models of CKD, both genetic and pharmacologic CDH11 inhibition improves renal function (BUN and proteinuria), diminishes cytokine production (TGF-β1 and IL-6 expression), and reduces tubular injury (KIM-1 and histological analysis). RNA-seq from AAN- and Unx/AngII-injured kidneys revealed that CDH11 knockout mice had significantly increased expression of alpha-1 antitypsin (A1AT) compared to wild type controls. Additionally, siRNA knockdown of CDH11 in immortalized PTs in vitro resulted in elevated expression of A1AT, confirming this mechanism in vitro. The protein inhibitor of A1AT has been used to promote PT survival in several kidney injury models. Using Cox proportional hazards models, we discovered that patients with A1AT mutations have increased incidence of CDK on a per-allele basis, with hazard ratios as high as 5.35.

Conclusions: These results establish CDH11 inhibition as a novel means of improving outcomes in murine CKD models and suggest an underlying mechanism of increased A1AT expression and enhanced PT survival. These findings advance our understanding of CDK and outline a new potential therapeutic strategy.

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SA-OR60
SARA in the Kidney: Regulation of Cell Phenotype as a Potential Therapeutic Target for Renal Fibrosis
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Background: Epithelial cells play an important role in renal fibrosis. After injury, podocytes and renal tubular epithelial cells (TECs) dedifferentiate. When dedifferentiated, podocytes detach from the glomerular basement membrane, while TECs stimulate surrounding cells to transdifferentiate into myofibroblasts, thus resulting in glomerulosclerosis and tubulointerstitial fibrosis respectively. Our laboratory has identified a unique protein called Smad Anchor for Receptor Activation (SARA) as a key factor for maintaining cellular phenotype in the face of fibrogenesis. Here, we aim to determine if SARA overexpression in podocytes and TECs can prevent their dedifferentiation and reduce fibrosis in mouse models of glomerulopathy and tubulointerstitial disease.

Methods: SARA overexpression was driven either by Podc4-Cre in podocytes (SARA+/− and Pax8-Rta, tet-O-Cre in TECs (SARA+/−) in mice. SARA negative littermates (Ctrl+/− and Ctrl+/+) were used as controls. SARA/Ctrl+/− mice were treated with Adriamycin to induce podocyte injury and SARA/Ctrl+/− mice with aristolochic acid (AA) to induce tubulointerstitial fibrosis. Urine, blood and kidneys were harvested for histological and molecular analysis. Markers for fibrosis and injury were measured by qPCR. Podocytes were isolated by flow cytometry from SARA/Ctrl+ mouse kidneys

Results: SARA+/− mice showed less glomerulosclerosis histologically and less proteinuria than Ctrl+/− mice after Adriamycin treatment. Tubular cell injury markers (KIM1, Sox9, NGAL) tended to be lower in SARA+/− mice compared to Ctrl+/− after AA treatment, but did not reach statistical significance. No significant difference in expression of markers of fibrosis was observed. Gene expression profiles of podocytes isolated from SARA/Ctrl+/− mice are being analyzed by RNA sequencing. This will provide insight into the mechanisms by which SARA maintains cellular phenotype and protects against renal fibrosis.

Conclusions: SARA overexpression protects podocytes and TECs against injury. Elucidating the mechanisms by which SARA functions will help unravel new molecular targets for therapies directed at glomerulopathies.

Funding: NIDDK Support

PO0001
Observational Evidence of NAD+ Biosynthetic Impairment and Urinary Metabolic Alterations in COVID-Related AKI
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Background: Acute kidney injury (AKI) is a frequent extrapulmonary manifestation of COVID-19 and is associated with increased morbidity and mortality. We investigated alterations in the urine metabolism associated with AKI among patients with COVID-19, with the hypothesis that changes in nicotinamide adenine dinucleotide (NAD+) metabolism described in ischemic, toxic, and inflammatory AKI will be also associated with AKI in patients with COVID-19.

Methods: This is a case-control study among two adult populations with COVID-19: critically ill patients hospitalized in Boston, Massachusetts, and a general hospitalized patient population in Birmingham, Alabama. Cases had AKI stages 2 or 3 by Kidney Disease Improving Global Outcomes (KDIGO) criteria. Controls had no AKI by KDIGO criteria. Metabolites were measured by liquid chromatography - mass spectrometry.

Results: 14 cases and 14 controls were included from both Boston, and 8 cases and 10 controls included from Birmingham. Urinary quinoline to tryptophan ratio, an indicator which increases with impaired NAD+ biosynthesis, was higher among cases than controls at each location and pooled across locations (median [IQR]: 1.34 [0.59-2.96] in cases, 0.31 [0.13-1.63] in controls, unadjusted p < 0.0013; p=0.03 in analyses adjusted for age and sex). We identified alterations in tryptophan, nicotinamide, and other components of energy metabolism as well as decreases in purine metabolites which contributed to a
distinct urinary metabolic signature that could reliably differentiate patients with and without AKI (supervised random forest class error: 1/14 for AKI and 1/14 for no AKI groups in Boston, 0.8% for AKI and 0/10 for no AKI groups in Birmingham).

Conclusions: Conserved urinary metabolic alterations spanning multiple biochemical pathways distinguish AKI vs. non-AKI in the context of COVID-related hospitalization at two large academic medical centers. AKI is furthermore associated with altered NAD+ biosynthesis that suggest impaired energy metabolism in the kidney. Augmenting renal NAD+ by administering biosynthetic precursors may present a novel therapeutic opportunity to mitigate COVID-19 associated AKI.

Funding: NIDDK Support, Private Foundation Support

PO0002

Expression of SARS-CoV-2 Viral Protein ORF3A in Renal Tubular Epithelial Cells Induces Injury

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Background: The coronavirus SARS-CoV-2 is the culprit of the COVID-19 pandemic. Acute kidney injury occurs frequently in COVID-19 patients and several lines of evidence suggest local infection of kidney cells by the virus. However, this remains controversial and it is unclear how the viral proteins of SARS-CoV-2 directly impact the health of renal tubular cells infected by the virus.

Methods: The viral protein ORF3A of SARS-CoV-2 was overexpressed in HK-2 renal tubular cell line and the proxenephric tubule epithelia of transgenic zebrafish. The NF-kB and STAT3 signaling pathways and target gene expression were analyzed using quantitative RT-PCR and Western blots. The expression of the renal injury marker Ki67 was also assessed by Western blots, quantitative RT-PCR and in situ hybridization. Protein interactions were studied by co-immunoprecipitation and Western blots.

Results: ORF3A augments both NF-kB and STAT3 signaling by enhancing the phosphorylation of the transcription factors and results in the expression of downstream target genes and subsequently increases the expression of kidney injury molecule 1 (Kim-1) in HK-2 cells. Mechanistically, ORF3A elevates the expression of TrpArip Motif-Containing Protein 59 (TRIM59), a ubiquitin E3 ligase, which forms a protein complex with ORF3A and STAT3. This in turn excludes the phosphatase TCPIP from binding to STAT3 and inhibits the dephosphorylation of STAT3. The transgenic zebrafish expressing ORF3A in renal tubular epithelia develop severe edema starting 48 hours post fertilization and in situ hybridizations shows elevated kim-1 expression in the proxenephric tubules, indicating that ORF3A induces renal injury in zebrafish in vivo.

Conclusions: The overexpression of ORF3A is sufficient to injure renal tubular epithelial cells and uncover a previously unrecognized molecular mechanism underlying the deregulation of STAT3 activity by ORF3A that leads to renal tubular cell injury, whether, the results of this study support the notion that direct infection of renal epithelial cells by SARS-CoV-2 may contribute to the renal complications in COVID-19 patients.

Funding: NIDDK Support, Clinical Revenue Support

PO0003

Deciphering the Impact of Cytokine Storm on APOL1 Expression in Primary Human Glomerular Endothelial Cells

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Background: High Risk (HR) Apolipoprotein L1 (APOL1) genotypes are associated with collapsing glomerulopathy in the context of interferons (IFNs), HIV, systemic lupus erythematosus (SLE), and SARS-CoV2 infection. Elevated circulating inflammatory cytokines, commonly referred to as “cytokine storm” are believed to play causal role in disease pathogenesis. Although the role of IFN and TNF in APOL1 induction has been described, it is unknown if other components of “cytokine storm” implicated in COVAN and lupus glomerulopathy also induce APOL1 expression. In vitro and animal studies show that expression of variant APOL1 is sufficient to cause glomerulosclerosis in dose-dependent manner. Therefore, it is important to establish if other components of “cytokine storm” regulate APOL1 expression in human glomerular compartment.

Methods: We evaluate the direct effect of cytokines implicated in the above diseases on APOL1 expression in primary human glomerular endothelial cells, a cell type with known significance in lupus and COVAN. We also screened these select cytokines using peripheral blood monocytes (PBMCs) from patient with SLE and HR APOL1 genotype.

Results: IFNγ (β=3.19), IFNα (β=3.08), and IL-1β (β=3.19) were the strongest drivers of APOL1 expression. Importantly, we also found that IL-6 increased APOL1 expression by 7 fold compared to control (p<0.01) in glomerular endothelial cells. Treatment with composite of all cytokines induced the most robust APOL1 expression. However, Jak 1/2-specific inhibitor, baricitinib, markedly attenuated this effect, with reduction in APOL1 expression from 800 fold down to 4 fold. Additionally, in PBMCs of a lupus patient with HR APOL1, IL-18 also showed significant upregulation of APOL1 expression.

Conclusions: Our data suggest that other cytokines beyond may be important in the pathogenesis of COVAN, HIVAN, and APOL1-associated lupus collapsing glomerulonephritis. It has been hypothesized that Jak-inhibitor may be a promising novel therapeutic strategy in these cytokine-mediated APOL1 nephropathies.

Funding: Other NIH Support - Common Fund (DP2, NIH Director New Innovator Award)

PO0004

Interferon-Activated Genetic Programs and a Novel Short Isoform of the SARS-CoV-2 Receptor ACE2 in the Kidney

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Background: Severe COVID-19 causes cytokine storm, worsening patient prognosis and contributing to acute kidney injury (AKI) development. Genetic programs activated in the renal epithelium by cytokines like interferon, as well as those abladed by JAK inhibitors, like ruxolitinib, were previously not investigated in detail. Additionally, a short isoform of ACE2, deltaACE2 (δACE2), of unknown function was recently identified as an interferon-stimulated gene, and it’s presence, inducibility and regulation in the kidney was not explored.

Methods: We treated Human Primary Proximal Tubule (HPTT) renal epithelial cells with IFNs, IFNγ, IL-18 and ruxolitinib and used RNA-seq to explore gene expression patterns. We performed GSEA analysis and compared this data to available AKI and renal COVID-19 datasets, as well as to other human interferon-treated tissues. We also measured mRNA expression of both ACE2 isoforms by RT-qPCR before and after cytokine stimulation and identified changes in gene regulatory elements of the ACE2 locus using ChIP-seq.

Results: RNA-seq analysis identified genes significantly induced by IFNγ (746), IFNγ (1169), IFNγ (1280) and IL-1β (2142), mostly immunity related. We saw an overlap of 162 genes between IFNγ treatment and the post-AKI dataset and of only 35 with severe COVID-19. Comparison of kidney, lung and liver cells treated with IFNγ revealed a shared set of 153 genes and unique 685 renal genes. Using RT-qPCR we show 300- and 600-fold upregulation of δACE2 mRNA by IFNγ and IFNγ, respectively, while full length ACE2 expression is almost unchanged. RNA-seq data revealed abundant fragment mapping to exons corresponding to δACE2 compared to rest of the transcript. ChIP-seq analysis showed additional putative regulatory elements in ACE2 locus using ChIP-seq.

Conclusions: We generated and made available novel RNA-seq and ChIP-seq data on human renal proximal tubule cells stimulated with cytokines. We observed that type 1 interferons significantly upregulated only the short isoform of SARS-CoV-2 receptor ACE2 and we linked it to JAK-STAT pathway, which may be an important factor in COVID-19 therapies using JAK inhibitors.

Funding: NIDDK Support

PO0005

Single Cell Analysis Reveals Deeper Insight of the Gateway Cell Type for SARS-CoV-2 in Kidney

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Background: Kidney injury is one of the extrapulmonary injury manifestations of COVID-19. Due to the specific expression of SARS-CoV-2 receptor angiotensinogenase 2 (ACE2), renal tubular epithelial cells are the main target cells of SARS-CoV-2 during kidney infection, although studies have found that the evidence of SARS-CoV-2 infection of glomerular cells. However, detailed mechanism of SARS-CoV-2 infecting kidneys still needs to be identified. Since mice don’t express ACE2, humanized organs have become important carriers for studying the mechanism of viral infection in vitro. It is still unclear whether the existing kidney organs are suitable for studying SARS-CoV-2 virus infection.

Methods: Data source: All scRNA-seq/bulk RNA-seq were downloaded from the Gene expression Omnibus. scRNA-seq analysis: The scRNA-seq was analyzed using Seurat R package. Cell communication analysis: Cell communication was analyzed using CellPhoneDB and Cellchat R package. SCENIC analysis: Gene regulatory network was analyzed using SCENIC R package. Bulk RNA-seq analysis: We used MuSiC R package to deconvolute bulk RNA-seq data. GSEA analysis: GSEA was performed using clusterProfiler package.

Conclusions: We identified a new cell type expressing high levels of the SARS-CoV-2 spike receptor ACE2 that is likely the gateway cell for viral entry, which is itself a progenitor for fibrocytes that produce abundant ECM, indicating that the kidney may have a critical role in SARS-CoV-2 disease progression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: We mined the available exRNA-seq dataset of human adult kidneys (GSE131882), and identified a proximal tubule subgroup. PTv cells, is susceptible to SARS-CoV-2 infection. PTv cells are highly enriched for a variety of factors related to viral infections (such as ACE2, DPP4, ANPEP, CTSB, TMPRSS2 etc.). Through cell communication and gene regulatory network analysis, we inferred that PTv cells are more active in other PT cells in terms of repairment, fibrosis, development, and reabsorption. Further by analysis in the datasets of GSE139061 and GSE126805, we found that the proportion of PTv increased during acute kidney injury, suggesting that PTv could be used to predict the progression of kidney injury. Analyzing human kidney organoid single-cell RNA-seq data (GSE119738, GSE115596, GSE108291, GSE147863, GSE119561, GSE114802, GSE136314, GSE118184), we identified that the PTv wildly present in kidney organoids, indicating that kidney organoids can be used in SARS-CoV-2 related research.

Conclusions: We revealed the characteristics of the PTv, a gateway cell for SARS-CoV-2 in kidney, and provided a molecular basis for the feasibility of renal organoids to study the renal tropism of SARS-CoV-2.

PO0006
Longitudinal Proteomic Characterization of AKI in Hospitalized COVID-19 Patients
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Background: Acute kidney injury (AKI) is a known complication of COVID-19 associated with increased in-hospital mortality.

Methods: We longitudinally measured serum levels of 4,497 proteins (SomaScan) in 437 COVID-19 patients at multiple timepoints along their hospital course and identified associations with AKI. Using single cell transcriptomic data from healthy human kidney specimens, we identified cell-specific kidney intracellular markers and quantified their leakage in sera from AKI patients. We also investigated whether serum proteomics impacts AKI prediction.

Results: We identified 408 upregulated and 107 downregulated proteins in COVID-AKI (144 cases, 293 controls, FDR<0.05, Fig 1A). Downregulated proteins included coagulation cascade inhibitors (protein C, heparin cofactor 2) and platelet dysregulation markers (Fig 1B), including platelet factor 4 (PF-4). Given the role of PF-4 in induced thrombocytopenia (HIT), we then retrospectively analyzed 4,035 COVID hospitalizations and found a significant association of HIT suspicion with COVID-AKI (aOR = 12.6, p <0.001). Intracellular AKI associated proteins were enriched for markers of the Loop of Henle, descending vasa recta endothelium, and NK cells (Fig 1C), which all have low ACE2 (Fig 1D) and TMPRSS2 expression (SARS-CoV-2 receptor and activator respectively), suggesting bystander damage within the kidney, not direct viral invasion likely drives COVID-AKI. Finally, a random survival forest model incorporating protein levels had lower prediction error for incident AKI than using only clinical variables (Fig 1E).

Conclusions: The COVID-AKI serum proteome is characterized by dysregulated platelets with clinical evidence of HIT, improves prediction of incident AKI in a machine learning model and suggests inflammation mediated renal cell death, rather than direct viral invasion via the renal ACE2 receptor.

Figure 1

PO0007
TIMP-2*IGFBP7 and N-Gal Are Strongly Associated with the Development of AKI in Patients with Severe Pneumonia Caused by SARS-CoV-2
Gustavo A. Casas-Aparicio, David Escamilla-Illanes, Departamento Investigacion Enfermedades Infecciosas - INER Instituto Nacional Enfermedades Respiratorias, Cuidad Mexico, Mexico.

Background: The cut-off points for the urinary kidney biomarkers (BM): TIMP2*IGFBP7 (Tissue Inhibitor of Metalloproteinase-2 *Insulin-Like Growth Factor Binding Protein-7 and Neutrophil Gelatinase associated lipocalin (NGal) in patients with AKI by SARS-CoV-2 are not defined.

Methods: Between May-August 2020 prospectively included patients with severe pneumonia caused by SARS-CoV-2 without AKI at the moment of enrollment. Fresh urine was collected at admission of critical care and was immediately frozen at -80 degrees Celsius. NGal and TIMP-2*IGFBP7 were measured in urine. We derived cutoffs based on sensitivity (S) and specificity (E) for predicting AKI using K-DEG criteria of urinary kidney biomarker BM and some serum BM. The best cut-off of N-Gal and TIMP-2*IGFBP7 were used to construct Kaplan Meier curves to assess differences in the risk of AKI. We performed a logistic regression model for significant variables to AKI. The analysis was conducted by SPSS V25.

Results: We included 51 patients, 20 AKI and 31 matched controls. Hypertension in the AKI group was 50% vs 12.9% p=0.009. Mortality in the group with AKI was 8 (15.7%) vs 2 NO-AKI (3.9%) p=0.013. Table 1 shows AUC of urinary and serum clinical BM for predicting AKI. TIMP2*IGFBP7 cut-off point of 0.2 ng/ml had S= 50%, E = 90%, and N-Gal 45 ng/ml had S=70.5%, E 80.6%. Survival curves for AKI were constructed after stratifying TIMP-2*IGFBP7 >0.2 vs <0.2 and N-Gal >45 vs <45 ng/ml, cut-off <0.2 of TIMP2*IGFBP7 had lower risk for AKI during (Log-rank test p = 0.002), lower risk for AKI was also observed with the cut-off <45 ng/ml for N-Gal (Log-rank test p = 0.001). Multivariable analysis indicated risk factor for AKI was higher when TIMP2*IGFBP7 >0.2 (ng/ml)/1000 (OR 10.29, 95% CI=1.26-83.60, p=0.029); and higher N-Gal >45 ng/ml (OR 5.57, 95% CI 1.00-30.87, p=0.038).

Conclusions: TIMP2*IGFBP7 and NGal in urine are excellent predictors of AKI in patients with severe pneumonia caused by SARS-CoV-2.

Funding: Government Support - Non-U.S.

Prediction of AKI using urinary and serum clinical biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>p</th>
<th>Sensitivity (S)</th>
<th>Specificity (E)</th>
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<td>TIMP-2*IGFBP7</td>
<td>0.897</td>
<td>0.021</td>
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<td>N-Gal</td>
<td>0.789</td>
<td>0.011</td>
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<td>Protein C</td>
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<td>0.012</td>
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<tr>
<td>Neutrophil Gelatinase associated lipocalin (NGal)</td>
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<td>0.015</td>
<td>0.613-0.928</td>
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<td>Tropinin</td>
<td>0.782</td>
<td>0.017</td>
<td>0.635-0.905</td>
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</tr>
</tbody>
</table>

AUC= Area under the curve

PO0008
AKI in a Mouse Model of COVID-19: Therapeutic Potential of a Novel ACE2 Variant
Laure Louise Hassler, Jan Wysocki, Anastasia Tomatisidou, Haley Gula, Vlad I. Nicolaescu, Isha Sharma, Glenn Randall, Yashpal S. Kanwar, Daniel Battle, Northwestern University Feinberg School of Medicine, Chicago, IL; The University of Chicago, Chicago, IL.

Background: We have previously shown that in the ischemia reperfusion model of AKI kidney ACE2 activity decreases and that the administration of a shorter soluble ACE2 variant markedly attenuates AKI in terms of GFR and kidney histology (Shirazi et al, ASN 2019). Here, we report the effect of a novel ACE2 variant designed to prevent/treat SARS-CoV-2 in transgenic k18-hACE2 mice infected with a lethal viral dose.

Methods: In a BSL-3 facility, transgenic k18-hACE2 mice were infected intranasally with 2x10^7 PFU SARS-CoV-2. ACE2 1-618-DDC-ABD was administered intranasally and intra-peritoneally 1 hour prior to viral challenge as well as 24 and 48 hours afterwards for a total of 3 doses. Infected control animals received PBS at the same time-points. Kidneys were removed from all animals and examined by light microscopy (LM) histologically and for apoptosis, using PAS and TUNEL staining, respectively.

Results: In mice infected with SARS-CoV-2, variable degrees of AKI were found by LM with the following features seen in the few most severe cases: proximal tubule brush border loss (black arrows, figure 1A and B), cytolysis (red arrow, figure 1A), tubular basement membrane disruption (blue arrows, figure 1A and B) and apoptosis (white arrows, figure 1A, B, D and E). In animals treated with ACE2 1-618-DDC-ABD, survival was near 100% and proximal tubular injury was absent or markedly attenuated with less proximal tubule injury (figure 1C) and minimal apoptosis (figure 1F). Glomeruli appeared ischemic (figure 1B, green arrow) but otherwise normal without evidence of thrombosis.

Conclusions: Kidneys from a transgenic mouse susceptible to SARS-CoV-2 infection, like patients with COVID-19, displays variable degrees of proximal tubular injury suggesting that this model can be useful to study AKI in COVID-19. Mice that received soluble ACE2 1-618-DDC-ABD protein were essentially protected from AKI suggesting a potential preventative/therapeutic role for soluble ACE2 in this otherwise pharmacologically untreatable devastating disease.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Kidney Injury Molecule 1 Is a Receptor for SARS-CoV-2 in Lung and Kidney

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Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first reported in Wuhan in 2019 and reached pandemic proportions. SARS-CoV-2-related respiratory failure and acute kidney injury (AKI) are major complications of infection. Kidney Injury Molecule-1 (KIM-1) is a scavenger receptor expressed by kidney epithelial cells and was previously reported to be a receptor for Hepatitis virus A. We hypothesized that KIM-1 is a receptor for SARS-CoV-2 and may play an important role in COVID-19 lung and kidney injury.

Methods: Human lung and kidney autopsy samples were immunostained and analyzed. Liposomal nanoparticles displaying the SARS-CoV-2 spike protein on their surface (virosomes) were generated. Virosome uptake by A549 lung epithelial cells, mouse primary lung epithelial cells and human kidney tubuloids (3D structures of kidney epithelial cells) was evaluated in the presence or absence of anti-KIM-1 antibody or TW-37, a small molecule inhibitor of KIM-1-mediated endocytosis that we discovered. Proteins of interaction characteristics between purified SARS-CoV-2 spike protein and purified KIM-1 were determined using mass spectrometry. HEK293 cells expressing human KIM-1 but not angiotensin-converting enzyme 2 (ACE2) were infected with live SARS-CoV-2 or pseudovirions expressing the SARS-CoV-2 spike protein.

Results: In mice, KIM-1 was expressed by kidney epithelial cells in COVID-19 patient autopsy samples. Human and mouse lung and kidney epithelial cells expressed KIM-1 and endocytosed spike-virosomes. Both anti-KIM-1 antibodies and TW-37 inhibited uptake. Enhanced KIM-1 expression by human kidney tubuloids increased virosome uptake. In both mouse and human cells, the EC50 for interaction between KIM-1 and SARS-CoV-2 spike protein and the receptor binding domain were 56.2±8.8 nM and 9.9±3.10 nM, respectively. KIM-1-expressing HEK293 cells without ACE2 expression had increased susceptibility to infection by live SARS-CoV-2 and pseudovirus expressing spike when compared with control cells.

Conclusions: KIM-1 is a receptor for SARS-CoV-2 in the lung and kidney and thus, KIM-1 inhibitors such as TW-37 can be potential therapeutics and or prophylactic agents for COVID-19.

Funding: NIDDK Support, Other NIH Support - NCATS, Government Support - Non-U.S.

Plasticity of Neutrophil Subsets in ANCA Vasculitis and COVID-19

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Background: A population of granulocytes appear in the PBM C layer of density separated blood and are termed Low Density Granulocytes (LDGs). These are seen in many conditions including cancer, sepsis, autoimmunity and pregnancy. We previously identified LDGs in acute and remission ANCA vasculitis (AAV) and hypothesise that these LDGs are also present in COVID-19 (C-19) and our aim is to phenotype these cells and determine whether LDGs are a disease specific cellular response to inflammation. Of particular interest is the expression of intracellular Arginase 1 (Arg-1), an enzyme linked to T cell suppression in many disease situations.

Methods: LDGs were isolated using a modified percoll preparation and analysed by both traditional and imaging flow cytometry, in patients with active and remission ANCA vasculitis, in patients with severe moderate and mild C-19 and in healthy controls. The phenotyping panel included CD14, CD15, CD16, CD53, CD33, CD626. Intracellular Arg-1 was stained following permeabilisation with saponin.

Results: We identified extensive populations of LDGs in both AAV and COVID-19 peripheral blood. LDG levels are associated with disease severity. Arginase 1 is differentially expressed in neutrophil populations from AAV and C-19. In C-19 Arginase levels are correlated to disease severity suggesting that Arginase release may be associated with favourable outcome. Interestingly, all neutrophil fractions show lower levels of Arginase in C-19 patients whereas in AAV only LDGs have lower levels. Healthy controls have high Arginase expression.

Conclusions: Neutrophil subsets display disease specific responses in C-19 and AAV demonstrating their plasticity in inflammatory settings and warrant further investigation.

Funding: Government Support - Non-U.S.

Plasma TNFFR1 Predicts Major Adverse Kidney Events in Hospitalized Patients with COVID-19

Steven Menezes,1 Steven G. Coca,2 Dennis G. Moledina,3 Yumeng Wen,4 Lili Chan,1 Heather Thiessen Philbrook,1 Wassim Obeid,5 Ewen U. Azeloglu,2 Brian P. Wilson,1 Chirag R. Parikh,1 TRIKIC Consortium: Translational Research Investigating Kidney Outcomes in COVID-19 ‘Johns Hopkins University School of Medicine, Baltimore, MD; 2Icahn School of Medicine at Mount Sinai, New York, NY; 3Yale University School of Medicine, New Haven, CT.

Background: Patients hospitalized with COVID-19 are at risk for major adverse kidney events (MAKE). Predicting which patients will experience progression of disease and poor outcomes remains elusive. We sought to develop a biomarker-based risk model for predicting MAKE in patients hospitalized with COVID-19.

Methods: We applied least absolute shrinkage and regression methodology (LASSO) to a prospectively enrolled cohort of 432 patients admitted with COVID-19 who had
blood specimens collected (median 2 days [IQR 2-4 days] from admission) from March 2020 to January 2021, at three large academic medical centers. Clinical variables and 26 plasma biomarkers were used as candidate features in the prediction models for the outcome of MAKE, defined as KDIGO stage 3 AKI, dialysis-requiring AKI, or in hospital mortality. Cross-validation was used for optimal shrinkage parameter selection and model tuning. Optimum optimism-corrected using bootstrapping.

**Results:** MAKE occurred in 85 (20%) patients within 60 days of admission. Application of LASSO to the 26 biomarkers selected IL-12, IL-13, IL-6, Tiel2, FGFL, NGAL, MCP1, YKL40, Ang1, Ang2, and TNFR1, which yielded an AUC of 0.88 (95% CI: 0.85-0.89) and was an AUC of 0.84 (95% CI: 0.82-0.89) when LASSO was applied on the clinical variables and TNFR1, 4 clinical variables (age, black race, obesity, WHO COVID severity score) and TNFR1 were selected with an AUC of 0.88 (95% CI: 0.87-0.89). Random Forest models of biomarkers and clinical variables had similar predictive performance. A cutoff of TNFR1 at 3005 pg/ml had a sensitivity of 69% (CI 0.85-0.91). Plasma TNFR-1 alone had an AUC of 0.88 (0.84,0.91). When LASSO was applied to plasma biomarkers were used as candidate features in the prediction models for the outcome of MAKE over 60 days. 

**Conclusions:** In this multi-center cohort study, plasma TNFR1 by itself produced a robust prediction for MAKE in patients hospitalized with COVID-19 that did not improve when combined with multiple clinical variables and was equivalent to combined inputs of 10 other plasma biomarkers.

**Funding:** NIDDK Support

PO0014


Kundan Jang, Kalyana C. Janga, Sheldon Greenberg. Maimonides Medical Center, Brooklyn, NY.

**Background:** Incidence of Acute Kidney Injury (AKI) among COVID-19 patients is 35%. Requirement for Renal replacement therapy (RRT) is estimated to be 15-20%. We aimed to identify risk factors associated with mortality and need for RRT in COVID-19 patients with AKI. We also estimated burden of the pandemic on inpatient hemodialysis (HD) unit.

**Methods:** Inpatients above 18 years, diagnosed with COVID-19 on RT-PCR between March-June 2020 were included in the study. AKI was defined using KDIGO guidelines. Data collected included demographics, serum creatinine, time to AKI, AKI, comorbidities, albuminuria and HD initiation. All inpatient HD sessions from January 1st, 2020 to June 2020 were included to estimate burden of COVID-19. CVVHD, PI RRT and PD were excluded. Statistical analysis included logistic regression, ANOVA, z-test for proportions and Chi-square test. Interrupted time series analysis using Auto Regression Integrated Moving Average (ARIMA) was used to predict proportion of bedside HD sessions from January 2020.

**Results:** 1991 patients positive for COVID-19 on RT-PCR were included. 683 (34.2%) were found to have AKI. 185 patients (27.1%) required RRT. Mortality among AKI patients was 64.7%. Age (OR=1.04; CI 1.03 to 1.06), AKI after 1 week (OR=2.15; CI 1.06 to 4.35), albuminuria (OR=2.57; CI 1.11 to 5.93), for need for RRT (OR=2; CI 1.26 to 3.19) and intubation (OR=4.6; CI 2.71 to 7.75) were the mortality risk factors. Albuminuria (OR=2.97; CI 1.04 to 8.46), CKD (OR=3.5; CI 1.67 to 7.34) and intubation (OR=7.8; CI 3.14 to 19.91) were the risk factors for RRT. Diabetes and hypertension did not increase mortality or the need for RRT. To estimate the burden of pandemic, 24086 HD sessions between Jan. 2016 to June 2020 were analyzed. Proportion of bedside HD was significantly higher in 2020 when compared to previous years (p<0.01) due to isolation interference. Sessions between Jan. 2016 to June 2020 were analyzed. Proportion of bedside HD sessions for 2020 between observed and expected values (p=0.01). Personnel requirement showed an extra burden of 870 nurse-hours with March-April accounting for 76%. This was due to increased number of bedside sessions requiring a 1:1 nurse-patient ratio as opposed to in unit session where nurse-patient ratio is 1:2.

**Conclusions:** Time to AKI, albuminuria and RRT are important risk factors for mortality in COVID-19 patients with AKI.

**PO0015**

Renal Comorbidities and New Acute Kidney Failure Drive Unfavorable Outcomes Among COVID-19 Positive Sickle Cell Trait Carriers

Sudha K. Iyerang,

Jessica Minnier,

Anurag Verma,

Shiuh-Wein Luoh.

**Million Veteran Program COVID-19 Disease Mechanisms Working Group ‘Lous Stokes Cleveland VA Medical Center, Cleveland, OH; Case Western Reserve University, Cleveland, OH; Biotistics Shared Resource, Knight Cancer Institute, Oregon Health and Science University, Portland, Portland, OR; VA Portland Health Care System, Portland, OR; Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Corporal Michael Crescenzo VA Medical Center, Philadelphia, PA; Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR; VA Portland Health Care System, Portland, OR.

**Background:** The sickle cell trait (SCT) in the hemoglobin beta gene (HbS; rs334) affects millions of Americans, especially African Americans (AAs) in whom alpha-thalassemia carriers (HbF: [MAF]=7%) and Hispanic Americans (HA; MAF=1%). We investigated the impact of SCT on the severity and sequelae of COVID-19 infection in the Million Veteran Program (MVP). Pre-COVID diseases and laboratory findings present in electronic health records (EHR), as well as acute events following 60 days of COVID-19 infection, and their effect on COVID-19 mortality among SCT patients were examined.

**Methods:** COVID-19 clinical data on genotyped MVP participants (SCT ~ 2,729, OR ~ 1.1 [1.42-8.4], p<0.01) was extracted from MVP. Outcomes analyzed were: severe disease (or mortality) vs. not severe (or survival). Ethnic-specific firth logistic regression for SCT was performed on European (EA), African (AA), Hispanic (HA) and Asian (ASA) groups, adjusting for sex, age, age^2, and 20 genetic principal components (PC) associated with ethnicity-specific admixture (PheWAS and LabWAS). For SCT captured 20+ years of comorbidities and historical laboratory values and was used to contrast effects of COVID-19. Multiple testing corrections were applied.

**Results:** Hbs is associated with increased COVID-19 mortality in AA (N=3,749; OR=1.1 [1.42-8.4], p<0.01) with a similar trend in HA. PheWAS revealed significant associations of rs334 with phlebitis for pulmonary embolism, chronic renal disease, diabetic kidney disease, hypertensive renal disease, gout, sickle cell disease/trait, and hemolytic anemia (FDR p < 0.1). After adjusting for SCT, past renal disease was significantly associated with higher COVID-19 deaths among AA. Increased incidence of acute kidney failure (AKF) and chronic kidney disease (CKD) were seen within 60 days of infection with COVID-19. We estimated direct and indirect effects of AKF or CKD in AA SCT carriers via a mediation framework. On average 20.7% (95% CI: 3.8% - 56.0%) of the total effect of SCT on COVID-19 death was found to be mediated through AKF, and that for CKD was 12.4% (95% CI: 6% - 63%).

**Conclusions:** SCT is associated with an elevated risk of mortality with COVID-19 infection. Both pre-existing chronic medical conditions and new acute events after COVID-19 may contribute to adverse COVID-19 outcomes with SCT.

**Funding:** Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**
Methods: 572 patients with confirmed diagnosis of COVID-19 (PCR) were evaluated. Our focus was on patients with pre-existing health conditions, serum parameters, and functional status were recorded. Statistical analysis and comparison between AKI-NRF and AKI-CKD patients were performed.

Results: From 720 individuals evaluated at the emergency room for suspicion of COVID-19, 572 of them were admitted with confirmed SARS-CoV-2 infection. Most of them were male (59%), median age 55 years, with hypertension (36%), obesity (25%), diabetes (18%), heart disease (5%), and COPD (9%). Almost all patients were robust (97%). 188 COVID-19 patients developed AKI (43%), although 149 (26%) presented a previous normal renal function (AKI-NRF), while 39 (7%) had CKD (AKI-CKD). Most of CKD patients (91%) developed AKI. There was a predominance of male gender, old age (a 60 years), frailty status (CFS ≥ 4), diabetes mellitus, obesity, COPD in AKI group (AKI-NRF and AKI-CKD subgroups) respect to NO AKI group (n: 380). The prevalence of hypertension and cardiac disease was significantly higher in AKI-CKD respect to AKI-NRF, and even higher respect to NO AKI. However, there was a tendency of higher mortality rate in AKI-NRF (69%) compared to AKI-CKD (56%). Even though, this trend did not reach statistical significance (p=0.09), mortality rate in AKI compared to NO AKI (16%) (p=0.0001) did. D-dimer was slightly higher in AKI-NRF compared to AKI-CKD (p=0.09).

Conclusions: There was a trend to higher mortality rate and D-dimer levels in AKI-NRF individual compared to AKI-CKD patients.

PO0018
AKI in Inpatients with COVID-19: Risk Factors and Mortality
Mauricio Ostrosky-Frid, Meredith C. McAdams, Pin Xu, Michael M. Li, Susan Hedayati. The University of Texas Southwest Medical Center; Dallas, TX.

Background: AKI in hospitalized patients with COVID-19 is a common adverse complication. Our aim was to investigate risk factors associated with AKI and whether AKI in this setting is independently associated with in-hospital mortality at 30 days.

Methods: All adult patients with confirmed SARS-CoV-2 PCR between March 3/21 to 1/21 to nineteen hospitals who had a COVID-associated billing diagnosis and no history of ESKD or kidney transplant were included. AKI was defined according to the Kidney Disease Improving Global Outcomes guidelines. Risk factors associated with AKI were evaluated using univariable and multivariable logistic regression, and mortality was evaluated using Kaplan-Meier and Cox Proportional Hazards models.

Results: The study cohort included 9,681 patients, of which 3,668 (38%) met criteria for AKI. Compared with patients without AKI, patients with AKI were older (median [SD] age 67 [16] vs 68 [18] years), more likely to be male (58% vs 47%), and more likely to be black (21% vs 15%). Patients with AKI were also more likely to have diabetes mellitus (52% vs 32%), hypertension (78% vs 57%), CKD (55% vs 17%), and coronary artery disease (20% vs 11%). Patients with AKI were also more likely to be on ACEI/ARB on admission (51% vs 37%), require mechanical ventilation (21% vs 3.2%) or have higher WBC, hs-CRP, ferritin, D-dimer, and cardiac troponin. P-values were <0.001 for all of the aforementioned comparisons. Risk factors significantly associated with AKI in the multivariable model included age, sex, race, hypertension, CKD, diabetes, ACEI or ARB on admission, mechanical ventilation, WBC on admission, hs-CRP, ferritin, d dimer, and troponin. Death occurred more frequently in patients with AKI (22%; n=811) than in those without (3%; n=178). Patient with AKI had higher mortality risk as compared to those without AKI, hazard ratio (HR) 3.08 (95% CI 2.56-7.1), that remained significant even after controlling for all variables associated with AKI, such as age, sex, race, comorbidities, inflammatory biomarkers, elevated troponin, and COVID-related treatments, HR 1.64 (95% CI 1.34-2.01).

Conclusions: Patients with COVID-19 who develop AKI have a higher mortality. We found that factors associated with AKI in the setting of COVID-19, and therefore increased mortality risk associated with AKI in COVID-19 is independent of these factors.

PO0019
Burden of AKI and CKD Among COVID-19 Survivors
Yan Xie, Benjamin C. Bose, Andrew K. Gibson, Evan Xu, Ziyad Al-Aly, VA Saint Louis Health Care System Clinical Epidemiology Center, Saint Louis, MO.

Background: COVID-19 is known to be associated with increased risk of acute kidney injury (AKI) during the acute phase of the infection. However, the burden of AKI and chronic kidney diseases (CKD) after the first 30 days of COVID-19 infection is not well known.

Methods: 181,384 COVID-19 patients from the United States Veterans Health Care System who survived the first 30 days of infection were enrolled and compared with 4,397,509 non-infected controls on burden of AKI and CKD at 6 months. Adjusted comparisons were conducted across severity of infection measured based on intensity of care received, and by subgroups based on age and pre-existing health conditions.

Results: With a median follow up of 150 (interquartile range: 115, 221) days, the adjusted excess burden of AKI due to COVID-19 was 6.07 (95% confidence interval: 5.46, 6.69) and excess burden of CKD was 7.19 (5.78, 8.55) per 1000 persons at 6 months. The excess burden of AKI increased with the severity of acute infection/excess burden > 12 (0.68, 1.36), 28.11 (25.94, 30.26) and 72.11 (67.53, 79.02) per 1000 persons at 6 months for COVID-19 patients without hospitalization, hospitalized and admitted to intensive care units, respectively). The excess burdens of CKD were 1.66 (0.19, 3.30), 36.41 (31.71, 41.11) and 82.55 (71.93, 93.78) for those not hospitalized, hospitalized and admitted to intensive care units, respectively. The burden of AKI and CKD increased with increased age (≥60, 60-70, >70 years) and increased pre-existing health conditions (Charlson comorbidity index of 0, 1-3 and >3) (Table).
Conclusions: Inflammatory markers (d-Dimer and procalcitonin) were associated with the development and severity of AKI but only septic shock was predictive of the development of AKI.

Comparison of socio-demographic in patients with SARS CoV-2 and AKI

PO0022
Impact of COVID-19-Associated AKI on Subsequent Development of CKD

Muner,1 Saigal,2 Bennett,1 Wisner,2 Abhijit,3

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Background: There is paucity of data about post-hospital discharge kidney-related outcomes in individuals with COVID-19-associated acute kidney injury (CoV-AKI) during the pandemic. We hypothesized that patients who survive a hospital admission due to COVID-19 and AKI are at risk for acquiring residual chronic kidney disease (CKD) thereafter.

Methods: We conducted a retrospective observational study examining records of patients hospitalized at Ochsner Medical Center over a 3-month period (March-May 2020) with COVID-19 and diagnosis of AKI by KDIGO. We examined the rate of full recovery of AKI (serum creatinine value back to within 10% of baseline or <1.2 mg/dL) at 9 months post-hospital discharge. Factors associated with recovery were assessed.

Results: Among 916 admissions due to COVID-19 within the study (220 (24%) to an intensive care unit), there were 226 (26%) cases of AKI, 96 of them (43%) with AKI requiring dialysis (AKI-KRT). Patients with CoV-AKI had a median age of 67 (34-99) and 58% were men. Self-identified black race accounted for 65% of the cohort. Among those with CoV-AKI, there were 111 in-hospital deaths (49%). Of 115 patients with CoV-AKI who were discharged alive, 9-month follow-up data were retrieved in 97 (missing data in 18). Full recovery of kidney function was achieved by 76 (78%). Among those who progressed to residual CKD, 11 (11%) patients were declared to have end-stage kidney disease (ESKD) requiring dialysis. Baseline CKD stages 3-5 was associated with lower rate of full renal recovery (23.76 (30%) vs. 14.23 (63%); RR: 2.01, p=0.004).

Conclusions: Full recovery from CoV-AKI was observed in ¾ of those who remain alive post-hospital discharge. About 1/10 of patients with CoV-AKI reached ESKD at intermediate-term follow-up. Preexisting CKD is associated with lower rate of recovery in CoV-AKI. These data do not seem to suggest that CoV-AKI is associated with greater risk for development of CKD compared to other forms of in-hospital AKI.

PO0023
Predictors of Recovery of Kidney Function Following AKI During Hospitalization for COVID-19

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Background: Studies have shown that COVID-19 hospitalization is associated with severe AKI. However, determinants of kidney function recovery for these patients are not well studied.

Methods: We conducted a retrospective analysis of patients admitted to our institution from March 2020 to April 2021 with diagnoses of COVID-19 and AKI. Recovery of kidney function was defined as a discharge creatinine less than 0.3 mg/dL above baseline. Data on patients’ demographics, comorbidities, AKI stage, ICU admission, and laboratory values were collected by chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with kidney recovery.

Results: Of 216 patients, the average age was 66.3 years and 56.0% were men. 62% of patients had recovery of kidney function by discharge. Univariate analysis identified independent factors such as severity of illness (ICU, p < 0.003), AKI-D (p < 0.001), AKI stage (p < 0.001), ICU admission (p < 0.001), and lower albumin (p < 0.040) as correlates of non-recovery at discharge. In the multivariate logistic regression model [(AUC: 0.732, 95% CI (0.68-0.800)], CHF (p = 0.011), AKI-2 (p = 0.011), AKI-3 (p = 0.001), and ICU admission (p = 0.060) remained associated with non-recovery (Table 1). Follow-up data, at a median of 64 days post-discharge, was available for 61% of the cohort (n = 131). Of these patients, 14% had new recovery after discharge, while 18% had no improvement compared to discharge. At 60 days post-discharge, 8.4% had new CKD. At discharge, 3% of all patients were dialysis dependent. Baseline CKD (p = 0.030) and CHF (p = 0.037) were associated with non-recovery at 60 days post-discharge.

Conclusions: Recovery from AKI Requiring Kidney Replacement Therapy in Critically Ill Patients with COVID-19

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Background: Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) occurs in as many as one in five critically ill patients with COVID-19. Expanding on previous work by this group, we examined the association of clinical factors at the time of KRT initiation with the outcome of kidney recovery at hospital discharge, accounting for the competing outcome of death.

Methods: We used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), a multicenter cohort study that enrolled adults with COVID-19 admitted to ICUs at 68 hospitals across the US from March 4 to June 22, 2020. Among those who acutely required KRT, the outcome of kidney non-recovery (continued dialysis dependence at hospital discharge) was explored with multinomial logistic regression, with kidney recovery (independence from dialysis at discharge) as the reference outcome and death as an alternate outcome. Exposures of interest included demographics, baseline medical status, and markers of illness acuity at the time of KRT initiation.

Results: Of 876 patients with AKI-KRT, 588 (67%) died, 95 (11%) survived to discharge and remained dependent on KRT, and 193 (22%) survived to discharge without KRT dependence. Patients with lower baseline eGFR had greater odds of kidney non-recovery, with OR 8.58 (95% CI: 3.03-24.28) among patients with eGFR ≤60. Reduced urine output on the day of KRT initiation was also associated with kidney non-recovery, with OR 4.23 (95% CI: 1.61-11.15) for urine output <50 mL/day vs >500 mL/day (Figure).

Conclusions: Among critically ill patients with COVID-19 with AKI requiring KRT, lower baseline kidney function and reduced urine output at the time of KRT initiation are associated with kidney non-recovery.

Funding: NIDDK Support

Table 1: Univariate and Multivariate Analysis of Predictors of Kidney Recovery

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0025

Critically Ill Patients with COVID-19 and AKI: Clinical Characteristics and Outcomes

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Background: Acute kidney injury (AKI) is a well-recognized complication of COVID-19. In this retrospective cohort study, we describe the clinical characteristics and outcomes of patients with severe COVID-19 in 8 intensive care units (ICUs) during the first wave of the pandemic.

Methods: Demographic, clinical, laboratory characteristics, and outcome data, including need for renal replacement therapy (RRT), mechanical ventilation, mortality, and RRT dependence at discharge and at 3 and 6 months, were extracted from the electronic medical record (EMR) between March and July 2020. Using nadir-to-peak serum creatinine, AKI and its stages were defined by the KDIGO consensus. Group comparisons were performed using ANOVA and chi square tests.

Results: After excluding 20 patients with end-stage kidney failure, 479 patients with severe COVID-19 were included. Table 1 displays the characteristics and outcomes of the cohort stratified by AKI. 409 (89.2%) patients developed AKI, with 194 (42.3%) developing stage-3 AKI. Male gender, white race, obesity, and COPD were associated with higher stages of AKI severity. 83 patients (18.1%) required RRT of which 27 (32.5%) survived, and 12 (44.4%) remained dialysis-dependent at hospital discharge. Follow up at 3-months and 6-months indicated dialysis dependence in 5 (45.5%) and 4 (36.4%) of 11 patients (1 died), respectively.

Conclusions: AKI is highly prevalent in our cohort and peak serum creatinine occurs within 3 days of intubation. Long-term dialysis dependence is of concern and merits further study. Multivariable analyses are under way to identify factors that are associated with severe AKI, need for RRT and in-hospital death.

PO0026

Increased Markers of Disease Severity in COVID-19 Patients with Hospital-Acquired vs. Community-Acquired AKI

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Background: The etiology of AKI in COVID-19 correlates strongly with age, comorbidities, and laboratory markers of disease severity. Outpatients with COVID-19 have different exposures that may cause AKI than hospitalized patients; thus, the etiology of AKI occurring before hospitalization [community-acquired AKI (CA)] may differ from those with hospital-acquired AKI (HA).

Methods: Excluding ESKD and hospital transfers, all COVID-19 PCR-confirmed cases admitted to 4 hospitals from 3/01/20 to 5/31/20 had data collected electronically through 7/31/20 including readmissions. Baseline C-EPI eGFR was determined by chart review for the period of 6 months prior to 5 months post-admission. AKI and recovery from AKI were scored using KDIGO staging. CA was defined as AKI with the highest level of creatinine (Cr) on admission, rising Cr on admission, or RRT started within 48 hours of admission without a subsequent AKI event after recovery. All AKI occurring > 48 hours was considered HA. To test which laboratory values correlated with CA or HA, we used a model adjusted for demographics, BMI, Elixhauser comorbidity index (ECI), and CKD stage.

Results: The table shows patients with HA and CA had similar demographics with only the ECI differing significantly. CA had less severe AKI, improved recovery to baseline, and lower mortality than HA. The lower mortality in CA was directly related to the lower stage of AKI. Within a given stage of AKI, mortality was not different between CA and HA. Recovery of renal function was significantly better in CA stage 1 vs. HA (5% vs. 26%, p = 0.001) but was not different for stage 2 or 3. In an adjusted model, higher
maximum dimers, ALT, AST, Bili, BNP, lactic acid, CRP, ferritin, LDH, neutrophils, troponin and lower minimum lymphocyte count were significantly associated with HA compared with CA. In contrast, on admission, only higher BNP, higher CRP, lower CPK and higher total CO₂ were associated with HA versus CA.

Conclusions: Compared to patients with CA, patients with HA had higher stages of AKI that correlated with higher mortality. They also had worsened recovery from stage 1 AKI and increased markers of COVID severity (except for CPK) in-hospital and on admission. We propose that factors other than COVID-19 disease severity led to CA, with volume and rhabdomyolysis as possible contributors.

PO0027
Hospital-Acquired AKI in COVID-19 Has a Similar Prognosis with or Without Prior Community-Acquired AKI
Emory Renal COVID-19 Project
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Background: Recent meta-analyses suggest that Hospital Acquired AKI (HA) has a worse prognosis than Community Acquired AKI (CA). The effect of prior CA on HA in COVID-19 is largely unknown. COVID-19 case series that use lowest hospital creatinine (Cr) rather than outpatient baseline Cr may underestimate CA incidence.

Methods: Excluding ESKD and hospital transfers, COVID-19 PCR confirmed cases admitted to four hospitals between 3/01/20 & 5/31/20 had data collected through 7/31/20 including readmissions. Baseline Cr was adjudicated by manual review from 6 months prior until 5 months post admission. AKI and renal recovery were scored using KDIGO staging. CA is AKI with the highest Cr on admission, rising Cr from admission, or RRT in 48 hrs of admission. HA is AKIs occurring after >48 hrs. HA with CA (HA+CA) is AKI occurring in CA patients after renal recovery for >48 hrs.

Results: AKI was present in 402/706 patients with COVID-19. HA+CA occurred in 63. Patients with HA+CA were older, had more comorbidities, lower eGFR, and lower admission albumin than patients with HA. Laboratory markers of COVID severity were similar in patients with HA or HA+CA and much worse than CA. Outcomes, including stage of AKI, renal recovery, ICU parameters, and mortality were similar in HA and HA+CA and much better in CA.

Conclusions: In COVID-19, HA + CA occurs in older patients with more comorbidities than HA but shares similar adverse disease markers and poor outcomes. We hypothesize that among older patients who recover from CA, those with severe disease markers are at risk for HA+CA.

Funding: Clinical Revenue Support

PO0028
Temporal Patterns in Incidence of AKI Associated with COVID-19 Using the National COVID Cohort Collaborative (N3C) Database
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Background: Acute kidney injury (AKI) is a common complication of patients hospitalized with coronavirus disease 2019 (COVID-19), however, the epidemiological studies are limited by single or few centers and short duration. How the incidence of COVID-19-associated AKI has changed over the last 18 months since start of the pandemic is not known.

Methods: We used the N3C enclave to collect data from 42 centers across 17 states and Puerto Rico, and 4,507 institutions across 28 states and Puerto Rico. Finally, 3,693,320 patients with a positive SARS-CoV2 PCR test admitted to 4 hospitals between 3/01/20 & 5/31/20 had data collected through 7/31/20 including readmissions. Baseline Cr was adjudicated by manual review from 6 months prior until 5 months post admission. AKI and renal recovery were scored using KDIGO criteria. Baseline Cr was defined from the outpatient values before hospitalization when available or lowest inpatient value if not available.

Results: Of the 103,471 patients hospitalized with COVID-19, 31,634 (30.6%) were diagnosed with AKI (mean age 63.3 years, 43.7% female, 19.5% Hispanic). 14,129 (13.7%) patients were diagnosed with AKI-1, 7,996 (7.7%) had AKI-2 and 9,509 (9.2%) patients had AKI-3 (6,285 [6.1%] without dialysis and 3,224 [3.1%] with dialysis). The incidence of 'all AKI' decreased from 38.8% in Dec 2019-March 2020 to 26.2% in March-May 2021 (p-value for trend = 0.086) and the incidence of AKI-3 declined from 15.5% to 6.5% (p = 0.086).

Conclusions: This is the largest and most nationally representative cohort of patients hospitalized with COVID-19 with the highest number of cases of AKI and of AKI-3 reported thus far. The incidence of COVID-19-associated AKI has shown a non-statistically significant decline during the past 18 months of the pandemic.

PO0029
AKI Prediction and Recovery in Hospitalized Patients with COVID-19
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Background: AKI is a complication in patients hospitalized with COVID-19 and is associated with poor outcomes. We aimed to develop predictive models for AKI development and recovery in patients hospitalized with COVID-19.

Methods: Patients with a positive SARS-CoV2 PCR admitted to 19 Texas hospitals from 3/13/2020 to 1/1/2021 were included. AKI presence and stages were determined using KDIGO guidelines. Individuals with AKI present on admission (POA) were excluded for predictive models. Patients were followed for 90 days to evaluate for renal recovery (serum creatinine ≤1.1 times baseline). Nested models for AKI were built using logistic regression: Model 1 included age, sex, race, smoking status, presence of hypertension and diabetes (HTN), diabetes, chronic kidney disease (CKD), coronary artery disease (CAD), and chronic heart failure (CHF); and use of ACEI/ARB; Model 2, added admission WBC, hs-CRP, and hemoglobin; Model 3, added ferritin and D-Dimer to Model 2 to assess for accuracy improvements. 10-fold stratified cross validation was done to evaluate model performance.

Results: Of 8392 patients, 2702 (32%) had AKI, of which 2281 (84%) recovered by 90 days: 92% of stage 1, 75% of stage 2, and 40% of stage 3 AKI. Of patients with AKI present on admission, 776 of 5671 developed AKI during the hospitalization. Percentages of AKI stages 1, 2, and 3 were 67%, 8%, and 25%, respectively. Overall, 152 (20%) of 776 required RRT. Patients with AKI were older, more likely to be male, black, and have hypertension, diabetes, chronic kidney disease, congestive heart failure, and CKD. The interval improvement of each AKI predictive model was statistically significant, with best model AUC of 0.77 (95% CI 76.3%-79.9%) and all p < 0.001. The final model had improvement in all metrics when compared to Models 1 and 2, with a sensitivity of 69%, specificity 76%, positive predictive value 32%, negative predictive value 94%, positive likelihood ratio 3.02, and negative likelihood ratio 0.40.

Conclusions: AKI is common among patients hospitalized with COVID-19, but a large proportion recover renal function by 90 days. Recovery rate is lower based on stepwise higher stages of AKI. Additional of inflammatory biomarkers to demographics and medical comorbidities can improve prediction of AKI in this patient population.
PO0030
Clinical Characteristics and Outcomes of COVID-19 Patients with AKI at Community-Based Hospital
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Background: The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and later called Covid-19 has resulted in significant morbidity worldwide. The virus can cause various complications and affect many organ systems. Preliminary reports have shown that Acute Kidney Injury (AKI) is common in patients with Covid-19, however, outcomes of kidney injury in hospitalized patients, especially at the community-based hospitals are not well described. The aim of this study was to describe the incidence, severity, and outcomes of Covid-19 patients with AKI at the community-based hospital.

Methods: This was a single-center, retrospective observational cohort study. All patients (age ≥18) with positive by polymerase chain reaction testing for Covid-19 who required hospitalization were included in the study. Mortality, Disease and kidney transplants were excluded. We compared outcomes of patients with and without AKI. We used univariable and multivariable Cox regression model to evaluate the relationship between AKI and in-hospital mortality.

Results: 220 patients were included in the study. 89 (40%) patients developed AKI, of whom 6 (7%) required Kidney replacement therapy (KRT) and 131 (60%) did not develop AKI. In-hospital mortality of patients with AKI was markedly higher than patients without AKI. Among the patients with AKI, 39 (43.8%) experienced in-hospital death while in patients without AKI, 23 (17.5%) died (P<0.001). Unadjusted HR was 2.01 (CI 1.23-3.14; P<0.001). The risk of in-hospital death remained significantly high following adjustment for baseline demographics and comorbidities with adjusted HR 1.8 (CI 1.50-2.74, P=0.015). The median hospital length of stay of patients who were discharged alive differed based upon AKI status. Patients with AKI-KRT had the longest median length of stay (15.5 days IQR 8.5-23.7), followed by patients with AKI non-KRT (7 days, IQR 5-14) and patients without AKI (6 days, IQR 4-10).

Conclusions: AKI is a common condition among patients hospitalized with Covid-19 and is associated with an increased risk of in-hospital mortality. It is important to consider this complication in the management of Covid-19 patients.

PO0031
Risk Factors for AKI and Mortality in COVID-19 in Western Mexico

Background: Acute kidney injury (AKI) in COVID-19 is associated with disease severity. The aim of this study was to identify risk factors associated with the development of AKI and its clinical impact, such as need for RRT and mortality.

Methods: Retrospective cohort study of hospitalized adult patients COVID-19, with normal kidney function, from April to December 2020 in Western Mexico.

Results: 882 patients (60.8% men) with a mean age of 58.9y were included. 342 (38.8%) had a prior diagnosis DM, 412 (46.7%) HTN, 161 (18.3%) obesity, 59 (6.7%) smoking history. 270 patients (30.6%) developed AKI, 95 (10.77%) KDIGO stage 1, 44 (4.98%) stage 2, and 84 (9.52%) stage 3. 59 patients required RRT (6.23%), and 111 (12.6%) stage 2 or 3 in-hospital mortality. Overall mortality was 30.6% (270 patients).

Conclusions: A high incidence of AKI in the Mexican population compared to reports from other countries, with a significantly high risk for death.

PO0032
Follow-Up Study of Survivors of Stage 2 or 3 In-Hospital AKI with or Without COVID-19
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Background: Acute kidney injury (AKI) is a hallmark of hospitalized patients with Coronavirus Disease 2019 (COVID-19) and associated with in-hospital mortality. Recent data suggests glomerular filtration rate (GFR) continues to decline after discharge in COVID-19 AKI survivors, but there are very few reports describing the long-term post-discharge outcomes.

Methods: This is an ongoing prospective study of 161 survivors of KDIGO stage 2 or 3 AKI who were admitted at Stony Brook Medicine (SBM) for COVID-19 between March–June 2020. ‘CKD’ was defined as patient’s final outpatient serum creatinine (Scr) value remaining >10% or 50% above baseline (defined as the lowest Scr during hospitalization) and final GFR < 60 ml/min/1.73m2. CKD was divided into ‘incident’ and ‘progressive’ based on baseline CKD status. We also investigated the readmission rate with and without AKI and post-discharge mortality. A comparison cohort of 66 AKI survivors concurrently admitted to SBM who tested negative for COVID-19 were also analyzed for all outcomes.

Results: COVID-19 AKI survivors were more likely to be non-White, Hispanic, have a lower prevalence of baseline CKD and greater severity of illness (mechanical ventilation, acute respiratory distress syndrome, vasopressor use and greater length of hospital stay) during hospitalization compared to COVID-19 negative survivors (p<0.01). COVID-19 negative AKI survivors were more likely to have re-hospitalization (p=0.03), although no difference was noted in re-hospitalization with AKI among the 2 groups. 29 out of 161 (18%) of COVID-19 positive AKI survivors died after their discharge from COVID hospitalization as compared to only 1 out of 66 patients (1.5%) of the COVID-19 negative AKI survivors (p=0.001). 42 (26.1%) of COVID-19 positive and 17 (25.8%) of the COVID-19 negative patients had a SCR and eGFR measure >90 days after discharge. COVID-19 positive AKI survivors (11.9-19.0%) had no difference in the rate of incident or progressive CKD compared with COVID-19 negative AKI survivors (11.9%). COVID-19 positive survivors of Stage 2 or 3 in-hospital AKI were more likely to have greater severity of illness during hospitalization and greater post-discharge mortality compared to COVID-19 negative AKI survivors. We did not find a difference in the rates of incident or progressive CKD at 10 months follow-up.

PO0033
Comparing COVID Acute Respiratory Distress Syndrome Patients on Extracorporeal Mechanical Oxygenation (ECMO) to Non-COVID Patients: Incidence and Effects of AKI
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Background: AKI has historically plagued those with ARDS and during the pandemic especially so with large resultant mortality rates. During thepast year these centers so equipped offered ECMO to treat severe COVID pneumonia. We compared the
non COVID ARDS requiring ECMO with patients with COVID pneumonia requiring ECMO. The aim of the study was to understand the difference in the renal outcomes and its effects of mortality and thereby help in prognostication.

Methods: This is a single center retrospective study where patients with COVID pneumonia needing ECMO in between March 2020 to April 2021 were compared with non COVID ARDS patients needing ECMO between April 2013 to April 2021. The 2 groups were compared and risk ratio calculated for the incidence of AKI, the need for Renal replacement therapy (RRT) and the mortality associated with it.

Results: After excluding the patients who did not meet the criteria, 26 COVID patients treated with ECMO were compared with 22 patients with non COVID ARDS treated with ECMO. The median age of COVID group was higher (48 years vs 36 years) and the median number of days needing ECMO for the COVID group was higher (13 days vs 31 days). Incidence of AKI and the AKI needing RRT were similar in the 2 groups. The overall mortality in patients with COVID pneumonia was higher. Patients with COVID who developed AKI had 1.32 times the risk of mortality, which increased to 1.62 when RRT was needed.

Conclusions: This is a first study comparing the renal outcomes of COVID ARDS requiring ECMO and non COVID ARDS requiring ECMO. Even though the median age and the median number of the days on ECMO were higher for the COVID group, surprisingly the incidence of AKI and those needing RRT were similar. But there was a significantly higher mortality when patients on ECMO developed AKI and even higher for those on RRT. This could be attributed to the cytokine storm seen with causing a multiorgan dysfunction which can present in the form of AKI. Presence of AKI needs to be identified early and can be used for the prognostication in COVID pneumonia.

PO0034
Rapid Deterioration or a Long Road to Recovery for COVID-19 Patients with AKI

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Background: Global reports on the rates, risk factors and outcomes of acute kidney injury (AKI) with COVID-19 exhibit high variability. We evaluated all patients admitted with COVID-19 and AKI from March 2020 to March 2021 in our hospital. Risk factors for poor outcomes including death. Methods: Retrospective study of all patients admitted with AKI between 13/03/2020 and 13/05/2020. All variables including COVID-19 status, demographics, co-morbidities and laboratory parameters were collected from electronic patient records. We used competing risk-regression models to assess association with mortality by subdistribution hazards ratio (SHR).

Results: Of 576 patients admitted with AKI, 257 (43.6%) were positive for COVID-19. Demographics and clinical characteristics of our cohort included: mean age 66.7 years, 58% male, 40.5% Caucasian, 56.3% hypertension, 33.1% diabetes. Overall 52.5% patients had AKI stage 1, 18.6% AKI stage 2, and 28.8% AKI stage 3. Patients with AKI stage 3 were 3.4 (95% CI 2.7–5.02) times more likely to be diagnosed with COVID-19 than those with AKI stage 1. Other factors associated with an increased likelihood of COVID-19 diagnosis adjusted for AKI stage were young age (p<0.004), non-Caucasian ethnicity (p=0.001), low lymphocyte count (p=0.002) and raised CRP, ferritin and D-dimer (p<0.001). Case fatality percentage of this cohort was 32.5% (10%, 19% and 35% mortality in COVID-19 negative patients with AKI stages 1, 2 and 3 respectively, compared with 33%, 52% and 71% in the COVID-19 positive counterparts). Patients with COVID-19 were 3.6 (95% CI 2.2-4.3) times more likely to die than those negative for COVID-19 (p<0.001). Furthermore, death in patients with COVID-19 and AKI stage 3 occurred rapidly, with 50% of patients dying within 10 days, 70% within 15 days and 95% within 21 days of admission. Those in the same group who survived had prolonged recovery, with 50% remaining inpatients in hospital for over 31 days.

Conclusions: In patients with AKI, those who were positive for COVID-19 was associated with severe AKI, younger age, non-Caucasian ethnicity, raised inflammatory markers, and suffered from high case fatality. Severity of AKI in conjunction with COVID-19 was associated with high and rapid death rates, or prolonged hospital admission with increased morbidity.

PO0035
Association of Endotoxemia with AKI in Critically Ill Patients with SARS-CoV-2 Infection

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Background: AKI is frequently complicated by sepsis. Endotoxin (lipopolysaccharide), a component of the outer wall of gram-negative bacteria, has been investigated and acknowledged as one of the triggers of lethal shock during sepsis and drivers of cytokine storm. In studies, septic shock was present in 6.4% patients with severe COVID-19, but blood cultures and respiratory cultures were negative in 76%. Initial cohort study of COVID-19 patients from China showed 4.5% developed AKI, subsequent reports showed higher prevalence. While these data suggest that patients with COVID-19 are at risk for septic shock and AKI, mechanisms mediating these processes in the setting of severe coronavirus 2 (SARS-CoV-2) infection remain unclear.

Methods: We conducted a single-center, cross-sectional study in critically ill patients with COVID-19 to test the prevalence of endotoxemia and whether endotoxemia is associated with the development of AKI. Patients were recruited using criteria: Age ≥ 18yr, MODS ≥ 1, sepsis and intensive care unit admission, excluded if pregnant, requiring chronic dialysis or chronic immunosuppressive medications. Blood endotoxin activity (EA) measured in patients who met the criteria using the FDA-approved Endotoxin Activity Assay (EAA). EAA is a chemiluminescent bio-assay based on the oxidative burst reaction of activated neutrophils to complement coated LPS-IgM immune complexes. Patients divided into low (0.0 – 0.39 EA units), intermediate (0.40 – 0.59 EA units), high (0.60 EA units), and non-responder (NR) (patients whose neutrophils do not have the ability to respond to performed immune complexes in the EAA) group based on measurements from the EAA.

Results: In this study, endotoxemia observed in 24/32 (75%) of our critically ill patients with COVID-19, despite only 2 patients having positive blood cultures for gram-negative organisms. The incidence of AKI was higher in the high EA group (7/14, 50%) as compared to intermediate EA group (1/10, 10%), p<0.001. The need for renal replacement therapy (RRT) was higher in the elevated EA group (4/14, 29%), with none of the patients in the intermediate group requiring RRT, p=0.008.

Conclusions: This study demonstrates the high prevalence of endotoxemia in critically ill patients with COVID-19, regardless of presence of bacteremia. We also observed that high EA was associated with AKI and the need of RRT.

PO0036
AKI in Extracorporeal Support

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Background: Acute kidney injury (AKI) is common in critically ill patients receiving extracorporeal membrane oxygenation (ECMO). Use of continuous renal replacement therapy (CRRT) with ECMO may help optimize fluid balance and correct electrolyte abnormalities but may also worsen outcomes. The relationship between AKI, CRRT, and survival in ECMO patients remains poorly defined. The aim of this study was to evaluate AKI outcomes in the setting of ECMO support. We assessed factors that may influence AKI severity, as well as the safety of combined CRRT with ECMO.

Methods: We performed a retrospective analysis of patients that received ECMO from 2018-2021 at a tertiary hospital, using a prospectively maintained database. All patients requiring CRRT received continuous veno-venous hemodialfiltration (CVVHDF). Data collected included demographics, ECMO and CRRT parameters, anticoagulation, baseline kidney disease, baseline serum creatinine (sCr), ECMO and CRRT duration, hospital length of stay (LOS), complications (patient and device-related), and outcomes.

Results: To date, 16 ECMO patients with AKI have been analyzed. Mean age was 48.6 ± 15.6 years. Eleven (68%) were male, and 50% were African American. ECMO indication included respiratory failure due to COVID-19 (43%), followed by respiratory failure from sepsis (19%). Initial ECMO modality was VV- in 75% and VA- in 25%. Mean baseline sCr and sCr at CRRT initiation were 1.3+/-1 mg/dL and 3.93+/-1.1 mg/dL, respectively. Mean ECMO duration was 30+/-37 days, and mean CRRT duration was 26+/-21 days. Elevated plasma hemoglobin (mean peak 103 mg/dL) levels occurred in 14 (88%) patients. Of 10 (63%) patient surviving to discharge, 3 (30%) were dialysis dependent. The incidence of AKI at CRRT initiation was 4.5%. AKI severity, as well as the safety of combined CRRT with ECMO.

Conclusions: Our results suggest that CRRT can be safely combined with ECMO to achieve satisfactory patient outcomes. Dialysis independence seems attainable in most patients; however, additional patient enrollment is underway to support this concept with a greater degree of confidence.
**PO0037**

**RAAS Inhibition and Risk of AKI in COVID-19**

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**Background:** Direct viral invasion of the kidney via ACE2 has been hypothesized as a mechanism of AKI in COVID-19 (COVID). The impact of RAASi on the risk of AKI in COVID is not known. We hypothesized that active use of RAASi preceding admission would be associated with a greater proportional risk of AKI in COVID than influenza (flu).

**Methods:** In this retrospective cohort, we compared the AKI incidence by RAASi status in 11,898 hospitalized Veterans with COVID or flu between Oct 1, 2019 and Sept 30, 2020. To control for confounding, propensity score weighting balanced baseline conditions, labs, and co-therapies in 4 exposure groups: RAASi users with COVID, non-users with COVID, RAASi users with flu, and non-users with flu. Weighted logistic regression estimated the main effects of RAASi and COVID, and their interaction.

**Results:** In flu, 7% of RAASi users had a stage 2-3 AKI vs 5% of non-users, a 2% increase (p=0.03). In COVID, 16% of RAASi users had a stage 2-3 AKI vs 12% of non-users, a 4% increase. While the absolute increase in AKI incidence for RAASi users vs non-users was greater in COVID patients vs flu, the difference was not statistically significant (p=0.66) and the RAASi association was proportionally smaller in COVID (see interaction in Table). Similar absolute differences were observed in stage 1-3 AKI (Table), and the interaction was also not statistically significant (p=0.66).

**Conclusions:** COVID was associated with a greater incidence of AKI than flu. RAASi was associated with an increased incidence of Stage 2-3 AKI in patients with COVID or flu. The proportional effect of RAASi was similar in COVID and flu patients. These findings do not support a disproportionate risk of AKI among RAASi users with COVID.

Funding: Veterans Affairs Support

AKI Incidence Rates and Odds Ratios in COVID and Flu by RAASi Status

<table>
<thead>
<tr>
<th>AKI Incidence Rates and Odds Ratios</th>
<th>COVID</th>
<th>Flu</th>
</tr>
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<tbody>
<tr>
<td>RAASi Users vs Non-users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1-3 AKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.16</td>
<td>1.00</td>
</tr>
<tr>
<td>Stage 2-3 AKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.56</td>
<td>1.00</td>
</tr>
</tbody>
</table>

IR: Incidence Rate, OR: Odds Ratio.

Rates and Stage 1-3 ORs are on the entire weighted cohort. Stage 2-3 ORs are in the subset of Stage 2-3 and no AKI patients.

**PO0038**

**Dexamethasone Reduces AKI in Critical COVID-19 Patients**


**Background:** More than 50% of severe COVID-19 patients develop acute kidney injury (AKI) and a high percentage of them will require renal replacement therapy (RRT). The aims of this study were to identify AKI prevalence and associated factors in patients with COVID-19 and invasive mechanical ventilation (IMV).

**Methods:** Prospective cohort analysis of all COVID-19 patients with IMV, admitted to our Institute in Mexico City (Mar 2020 - Jan 2021). AKI was defined according to KDIGO guidelines. Patients with CKD stages 4 or 5 were excluded. Demographic, clinical, laboratory, and treatment variables were registered. AKI development was analyzed by uni- and multivariate logistic regression, mortality by survival analysis.

**Results:** Of 552 COVID-19 patients, AKI was detected in 196 (35.5%). Among AKI; 80 (40.8%) were Stage 2, and 116 (50%) Stage 3. The incidence of each AKI stage was lower in patients treated with dexamethasone (DEXA, Fig. 1A) and decreased the requirement of RRT (30 vs 16, p=0.05). For the multivariate analysis, AKI was grouped into no AKI/Stage1 and Stage 2-3 AKI; DEXA treatment was associated with less AKI incidence (OR 0.34, 95%CI[0.23-0.51]) and lower mortality in the adjusted Cox-regression analysis (Fig. 1B).

**Conclusions:** AKI is associated with increased mortality in COVID-19 patients with IMV. The use of DEXA is associated with lower AKI severity and lower mortality.

**PO0039**

**Volume Balance and AKI in Critically Ill Patients with SARS-CoV-2**

Samantha Crumming, Ashley La, Anthony Hung, Daniel S. Rubin, Jay L. Koyner. University of Chicago Division of the Biological Sciences, Chicago, IL.

**Background:** Evidence from the management of critically ill patients suggests restrictive volume management strategies and avoidance of volume overload improve ICU outcomes. Restrictive practices have been applied to the management of patients with SARS-CoV-2 (COVID-19), but data describing volume management and its associated outcomes in those with and without acute kidney injury (AKI) in this setting are lacking.

**Methods:** We conducted a single-center retrospective cohort study of ICU patients with COVID-19. 7-day cumulative volume balance from ICU admission in excess of 5% (negative balance) or +5% (positive balance) of ICU admission weight as well as AKI based on KDIGO guidelines were identified. Associations between volume balance, AKI and clinical outcomes (dialysis, mechanical ventilation, and inpatient mortality) were explored.

**Results:** 194 of 374 ICU admissions (51.9%) had AKI with 60 of 374 (14% (16.0%, 30.9% of those with AKI) requiring dialysis. 110 of 374 (29.4%) developed negative balance and 40 of 374 (10.7%) developed positive balance. Inpatient mortality was significantly higher in those with AKI compared to those without AKI (p=0.048). Using the Kaplan-Meier estimator, patients with no AKI had no difference in inpatient survival when compared on the basis of volume balance (p=0.69). However, in those with AKI, inpatient survival was significantly lower for positive and negative volume balance compared to neutral balance (p=0.01).

**Conclusions:** Negative and positive volume balance are associated with higher inpatient mortality particularly in patients with AKI. Future research must investigate the impact of negative balance on morbidity and mortality in patients with and without AKI.

**Outcomes of ICU Patients with Negative Balance by AKI Status**

<table>
<thead>
<tr>
<th>AKI Status</th>
<th>Negative Balance (%)</th>
<th>Positive Balance (%)</th>
<th>Neutral Balance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI</td>
<td>16.0%</td>
<td>7.2%</td>
<td>16.0%</td>
</tr>
<tr>
<td>AKI</td>
<td>29.4%</td>
<td>10.7%</td>
<td>30.9%</td>
</tr>
</tbody>
</table>

**PO0040**

**Urinary Findings Reveal Dominant Tubular Injury in Hospitalized Patients with COVID-19**

Avital Angel-Korman,1 Adi Leiba,1,2 Samson Assuta University Hospital, Ashdod, Israel; 2Ben Gurion University, Faculty of Health Science, Beer-Sheva, Israel.

**Background:** Renal manifestations during infection with SARS-CoV-2 are prevalent and include proteinuria and hematuria as well as acute kidney injury (AKI). Possible mechanisms of renal involvement with COVID-19 are acute tubular injury (ATI) due to cytokine storm, direct virus-induced tubulopathy or glomerular injury related to podocytopathy. However, a kidney biopsy or urine studies including direct urine microscopy have rarely been performed. Our aim was to examine the urinalysis, level of...
protein excretion and microscopy findings in urine from hospitalized COVID-19 patients in order to better elucidate the nature of COVID-19 related kidney involvement.

**Methods:** We collected fresh urine samples from 92 patients admitted to the COVID-19 ward at Samson Assuta University Hospital in Israel. Urine samples were collected randomly, regardless of renal function or prior medical history. Urinalysis and urine chemistry were performed in addition to direct urine microscopy analyzed by an experienced nephrologist.

**Results:** Urine samples were collected from 55 men and 37 women, most of whom (64%) had severe COVID-19 at the time urine samples were obtained. AKI at different levels of severity was diagnosed in 37 patients (40%). Proteinuria and hematuria were present in 43% and 38% of urinalysis samples, respectively, suggesting glomerular involvement. Urine protein to creatinine and albumin to creatinine ratios were measured in 76 patients (83%). Median urinary albumin to protein ratio (UATPR) was very low (~0.16), indicating a tubular origin of the proteinuria. Direct urine microscopy was performed on 58 samples, of which granular casts were detected in 43% (25 samples) and in 5 of them granular casts were spotted without evidence of AKI. Additionally, uric acid crystals and amorphous urate were found in 19 (33%) of microscopy samples. Median urine pH was 5.5 which likely contributed to precipitation of uric acid. Notably, urine sediment clues of either nephrotic or nephritic syndrome were absent in all examinees.

**Conclusions:** Urinary sediment findings and a very low UATPR support ATI as the main mechanism for kidney injury in COVID-19 patients. Acidic urine and uric acid crystals may have resulted from viral related ACE2 down regulation, enhanced angiotensin II and aldosterone mediated urinary acidification. Further studies are needed to shed light on COVID-19 related kidney involvement.

**PO0043**

**Clinical Outcome and Antibody Response in COVID-19-Positive Pediatric Kidney and Liver Transplant Recipients**

Efrat Talgam Horshi, Yael Mozer Glassberg,2,3 Orth Waibourd-Zinnmann,2,3 Liat Ashkenazi-Hoffnung,2 Orly Haskan,2 Shelly S. Levi,2,3 Gilad Hamdani,2,3 Daniel Landau,2,3 Hadas Alfandary,2,3 Assuta Ashdod Hospital, Ashdod, Israel; 1Schneider Children’s Medical Center of Israel, Petah Tikva, Israel; 2Tel Aviv University Sacker Faculty of Medicine, Tel Aviv, Israel.

**Background:** The COVID-19 pandemic has profoundly impacted transplantation activity worldwide. Nevertheless, data on the clinical and laboratory features of SARS-CoV-2 infection in pediatric recipients of solid organ transplant (SOT) recipients are scarce.

**Methods:** We describe clinical and laboratory manifestations, including serologic response, and short-term outcomes of 25 pediatric recipients of SOT who tested positive for SARS-CoV-2 during the first nine months of the epidemic in Israel.

**Results:** The mean age was 15.2±4 years; 14 (56%) were kidney and 11 (44%) liver transplant recipients. Twenty-three (92%) of the patients were symptomatic. The most common symptoms were fever (44%), headache (44%), cough (40%), and fatigue (36%). Most (84%) had a mild disease. Two patients (8%) had a moderate disease. Eight patients (32%) had a severe disease. Twenty-three (92%) of the patients were symptomatic. The most common symptoms were fever (44%), headache (44%), cough (40%), and fatigue (36%). Most (84%) had a mild disease. Two patients (8%) had a moderate disease. Eight patients (32%) had a severe disease. Twenty-three (92%) of the patients were symptomatic. The most common symptoms were fever (44%), headache (44%), cough (40%), and fatigue (36%). Most (84%) had a mild disease.

**Conclusions:** Our study demonstrated that while the majority of pediatric recipients of SOT developed a mild disease with a positive serologic response, a relatively high percentage (8%) developed a severe disease. This emphasizes the need for close monitoring of this particular population, especially those with comorbidities.
COVID-19 Seropositivity in New York ESKD Patients
Ranjita Chand, David M. Charytan, Lama Nazzal, Amay Mishra, Mansi Mehta, Robert Holzman. NYU Grossman School of Medicine, Division of Nephrology, New York New York University, New York, NY.

Background: Patients on hemodialysis (HD) with COVID-19 infections have increased emergency room visits, hospitalization, and mortality. We evaluated COVID-19 seroprevalence in a dialysis association in NYC.

Methods: We collected data on patients undergoing maintenance HD in four different units in Manhattan, New York. Data was collected regarding demographics, cause of kidney failure, time on dialysis, and insurance. Covid antibody was tested using the elecsys Anti-SARS-CoV-2 immunassay. We performed univariate analysis using Chi square test and multivariate linear logistic regression models to identify variables associated with COVID-19 seropositivity.

Results: Seropositivity was detected in 108 (20.2%) out of the 535 patients tested. In univariate analysis, age, HD unit, race, institutionalization status, time on dialysis, and type of insurance were associated with seropositivity. In multivariate analysis race, age, time on dialysis were not associated with COVID seropositivity. Patients uninsured, or those covered by medicare, had a significantly higher likelihood of testing positive for COVID antibodies than patients covered by private insurance (OR, 8.02, P=0.005). In reference to the Chinatown unit, patients receiving treatment at the 34th Street unit (OR, 4.90, p=0.002) and the Lower Manhattan unit (OR, 3.42, p=.02) were more likely to test positive. Institutionalized patients were almost eleven times more likely to test positive for the antibodies than those not institutionalized (OR, 10.97, p<0.001). Race was not significantly associated with antibody positivity.

Conclusions: Our study showed increased prevalence of COVID-19 antibodies in Institutionalized and uninsured/Medicaid patients but no association with race suggesting socioeconomic status, is more important than race in determining the risk of COVID-19 infection in patients on maintenance dialysis.

Prevalence and Dynamics of SARS-CoV-2 Nucleocapsid IgG in Kidney Transplant Recipients
Harith Al Raees, Pablo Loarte Campos, Cindy T. Pynadath, Omar Alani, Harith Raees, Luz E. Liriano-Ward, Maria Ajaimy, Enver Akalin. Montefiore Medical Center, Bronx, NY.

Background: We aimed to investigate the prevalence and dynamics of SARS-CoV-2 IgG in kidney transplant recipients in the Bronx, New York, one of the epicenters of the pandemic.

Methods: Between March 16 and May 5, 2021, 255 patients tested positive for SARS-CoV-2 RT-PCR. From May 3 to May 5, 2021, 1,164 patients were screened for SARS-CoV-2 IgG antibodies and 199 (17.1%) were tested positive (Figure).

Results: 62 of the 199 patients were previously diagnosed COVID-19 by RT-PCR, while the remaining 137 did not have significant symptoms and had not been previously tested by RT-PCR. Overall prevalence of COVID-19 diagnosis by RT-PCR and/or SARS-CoV-2 IgG in 1,348 patients tested was 29.1%. Seventy-one RT-PCR+ patients were positive for the antibodies than those not institutionalized (OR, 10.97, p<0.001). Race was not significantly associated with antibody positivity.

Conclusions: Our study showed increased prevalence of COVID-19 antibodies in Institutionalized and uninsured/Medicaid patients but no association with race suggesting socioeconomic status, is more important than race in determining the risk of COVID-19 infection in patients on maintenance dialysis.

Dana Mueller,1,2 Angela Pauline P. Calimag,1,2 Anthony Guglielmi,1,2 Caroline Youssouf,1,2 Spencer Delevaux,1,2 Vinay Raju,1 Edgar V. Lerma,1,2 Advocate Christ Medical Center, Oak Lawn, IL; 1University of Illinois at Chicago, Chicago, IL.

Background: Acute kidney injury associated with COVID-19 is poorly understood; majority of the published literature currently available in the United States comes from major academic institutions. This study aims to describe the epidemiology and general outcomes of hospitalized patients with COVID-19 at a large tertiary community hospital.

Methods: This is retrospective descriptive study of the incidence of acute kidney injury for hospitalized patients with COVID-19 between March 1st - May 31st at a major academic institution. This study aims to describe the epidemiology and general outcomes of hospitalized patients with COVID-19 at a large tertiary community hospital.

Results: Of the 684 patients admitted the hospital with COVID-19 infections, 231 (33.8%) developed an AKI. Stage 1 129 (55.8%), Stage 2 36 (15.6%), Stage 3 66 (28.6%). Urine microscopy showed proteinuria 104 (45.1%), hematuria 129 (55.8%), leukocyturia 129 (55.8%); Median FE Na 0.7 [0.1 - 0.7] and FE Urea 21.1 [15.0 - 29.5].
Renal biopsy performed on four patients demonstrated acute tubular necrosis. Fifty-two (13.1%) patients required KRT. Nine (3.9%) went hospice, and 72 (31.2%) died. One patient was still in hospital as of discharge. 138 (59.7%) were discharged without KRT, whereas 12 (5.2%) patients were still hospitalized. AKI 15.0 [7.1 - 27.2] days p < 0.01). Most common co morbidities were Type 2 diabetes and hypertension. D-dimer, LDH, CRP, procalcitonin and IL-6 were significantly higher. Upon discharge, 138 (59.7%) were discharged without KRT, whereas 12 (5.2%) patients required KRT. Nine (3.9%) went hospice, and 72 (31.2%) died. One patient was still in hospital as of discharge.

**Conclusions:**
Acute kidney injury is a poor prognostic indicator for patients with COVID-19. The mortality rates and outcomes of patients with AKI in this setting are comparable to previously published studies.

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**PO0048**  
**Kidney Recovery Post Coronavirus Infection in Hospitalized Kidney Transplant Recipients: A Single-Center Observational Study**  
Adarsh Vijay, Gina L. Defelice, Kofi ATIemo, Hoonbae Jeon, Mary Killacky, Sixto G. Giusti, Anil S. Paramesh. Tulane University School of Medicine, New Orleans, LA.

**Background:** Kidney transplant recipients (KTR) are at an increased risk of severe disease and death caused by coronavirus-19 infection. There is a paucity of information on the evolution of graft function among hospitalized KTRs who overcome the infection.

**Methods:** The study included adult KTRs at a single transplant institute who were diagnosed with Coronavirus-19 virus and needed hospitalization between March 15, 2020 and January 15, 2021. We analyzed patient demographics, comorbid risk factors, and inpatient clinical course for patients who were able to recover from the infection. Kidney function was analyzed pre-infection, during initial hospitalization and up to 12 months post infection.

**Results:** We identified 48 kidney transplant recipients who were diagnosed with Coronavirus-19 infection during the study period. Eighteen KTRs among these needed hospitalization for symptoms of fever and respiratory distress. Four patients died of Coronavirus-19 infection related complications and were excluded from the study. The 14 remaining patients in the study were predominantly black (78%), with a median time since transplant of 4 years. 64% of the patients developed AKI, with an average peak serum creatinine of 2.64 mg/dl and GFR of 34. The mean serum creatinine and GFR of the group were 2mg/dl and 44 at baseline (prior to infection). This represented an increase in their serum creatinine and GFR of 34% and 29% respectively. The median follow-up post infection was 7.5 months. The serum creatinine and GFR of KTRs were 4.83 mg/dl and 48 at 3 months, and 2.2 mg/dl and 40 at 6 months post infection. New onset proteinuria was noted in 5 out of the 14 patients (36%), with complete resolution of same in all at 3 months follow up. 75% patients with AKI had complete recovery at 3 months follow-up. The median baseline GFR of patients who had incomplete recovery was 32. There was only 1 graft loss and this was in a patient who had chronic rejection and had a baseline Cr of 3.8 mg/dl at time of coronavirus infection.

**Conclusions:** AKI is common among KTRs that are hospitalized with Covid-19 infection. Most of these recover, although we noted that patients with baseline lower kidney function (GFR < 32) and existing proteinuria had a lower recovery rate.

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**PO0049**  
**Risk Factors for Mortality in Patients with COVID-19-Related AKI in São Paulo, Brazil**  

**Background:** In COVID-19, as in SARS, the degree of kidney injury can have major implications for the clinical outcomes. Early reports indicate that, among patients with COVID-19, AKI is common and is associated with worse outcomes. However, COVID-19-related AKI among ICU patients in Brazil has not been well described.

**Methods:** This was a retrospective observational study of the electronic health records of patients with COVID-19-related AKI admitted to the Hospital das Clínicas in the city of São Paulo, Brazil, between March and August of 2020. We applied only KDIGO criteria 2 and 3. We used logistic regression to analyze risk factors for the composite outcome of mortality or RRT.

**Results:** Among the 694 patients with COVID-19-related AKI, the mean age was 63 years and mortality was 66%. 41% needed vasopressor drugs, 66% needed mechanical ventilation, and 72% needed dialysis. Univariate analysis showed the following risk factors for mortality and RRT at admission: male sex; diabetes; CKD; vasoactive drug use; mechanical ventilation; acidemia; elevated lactate, magnesium, potassium, creatinine, C-reactive protein, creatine phosphokinase, total bilirubin, proteinuria, hematuria, and increased fractional excretion of potassium (n=98) and sodium (n=110). The factors that remained significant in the multivariate analysis were male sex, vasoactive drug use, serum magnesium >2.5 mg/dl and oliguria (24-hour urine output <500 mL).

**Conclusions:** In COVID-19 related AKI in Brazil and elsewhere, in-hospital mortality is high. The exact mechanism by which hyperglycaemia increases mortality in such patients merits further study. Supported by FAPESP.

**Funding:** Government Support - Non-U.S.
Associations of Dialysis Modality and Setting with Incidence of COVID-19 Diagnosis and Hospitalization

Eric D. Weinhandl,1,2 David T. Gilbertson,1 James B. Wtemore,1 Kirsten L. Johansen,1 Hennepin Healthcare Research Institute, Minneapolis, MN; 1University of Minnesota Twin Cities, Minneapolis, MN.

Background: The novel coronavirus 2019 (COVID-19) pandemic has resulted in substantial morbidity and mortality among patients undergoing maintenance dialysis. Patients performing home hemodialysis (HHD) or peritoneal dialysis (PD) may be able to minimize exposure to the community, thus lowering risk of COVID-19 infection. We assessed whether HHD and PD were associated with lower risks of COVID-19 infection and hospitalization, compared to in-facility hemodialysis (IFD).

Methods: We analyzed Medicare Parts A and B claims accrued during 2020. For each epidemiologic week from week 12 (beginning March 15) to week 37 (September 6), we identified patients with a Medicare-covered outpatient dialysis treatment during the preceding 7 days. We stratified patients into cohorts of IHD, HHD, and PD; we limited the IHD cohort to patients without residency in a skilled nursing facility during the 28 days preceding the epidemiologic week. During each week, we estimated the incidence of COVID-19 infection and COVID-19 hospitalization, per Medicare claims with ICD-10-CM diagnosis code U07.1. Using logistic regression with adjustment for demography, comorbidity, and state, we estimated odds ratios of outcomes during weeks 12-22, 23-33, and 34-37.

Results: Incidence of COVID-19 infection (figure) and COVID-19 hospitalization peaked twice: during weeks 14-16 and weeks 29-30. During weeks 12-22, adjusted odds ratios (AORs) of COVID-19 infection for HHD versus IHD and PD versus IHD were 0.55 (95% CI, 0.43-0.71) and 0.52 (0.46-0.58), respectively. During weeks 23-33, peak was between 2020-June 2020 to better understand COVID-related mortality in SI and not SI patients.

Methods: We restricted to 6 dialysis centers (6 in NYC, 3 in Denver, CO, and 1 in Dallas, TX) with 1,507 patients. Dialysis staff screened patients monthly with the surprise question (SQ)—"Would I be surprised if this patient died in the next 6 months?"—and recorded outcomes. Those with a "No" response were identified as SI. A SQ "No" response is known to identify older patients with multiple comorbidities and an increased risk of early mortality. In this rolling population, we calculated the monthly mortality risk prior to and during COVID and determined the relative risk of death (RR) for SI compared to not SI during both periods. We also compared the increased mortality risk during COVID between patients dialyzed in NYC vs. Denver and Dallas and used logistic regression to determine whether COVID-19-related mortality differed by geographic region.

Results: Over 14 months, dialysis centers screened a monthly average of 1,342/1,507 (89.1%) patients and identified 274 (18.2%) as SI, with more consistent screening pre-COVID than during COVID (98.6% vs. 71.2%). Pre-COVID, the monthly mortality rate for SI patients was 2.8% and for not SI patients 0.4% (RR 7.02, 95% CI 4.76-10.44). During COVID, the monthly mortality rate for SI patients increased to 4.8% and for not SI to 1.5% (RR 3.19, 95% CI 2.28-4.44). The absolute increase in monthly mortality risk from pre-COVID to COVID was greater for SI than for not SI patients, 2.0% vs 1.1%. The excess monthly mortality was higher in NYC (2.5% for SI and 1.2% for not SI) than in Denver and Dallas (1.3% for SI and 0.7% for not SI), but the difference was not significant (p = .12).

Conclusions: A "No" response to the SQ identified SI dialysis patients whose 5-month mortality during COVID increased to 23.9% (annualized rate 57.4%). For not SI, the 5-month mortality rate during COVID increased to 7.5% (annualized rate 18%). These findings underscore the importance of advance care planning not only for SI patients but also for all dialysis patients, who are particularly vulnerable to concurrent infections such as COVID-19.

Funding: Private Foundation Support

Temporal Trends in Mortality and Hospitalization Related to SARS-CoV-2 in Dialysis Patients in Quebec (Canada)

Amicie-Claire Nadeau-Fredette,1,2 William Beaubien-Souligny,1 Fabrice Mac-Way,1 Remi Goupil,1 Daniel Blum,1 Rita Suri.2 For the Quebec Renal Network Study Group 1Hôpital Maisonneuve-Rosemont Centre de Recherche, Montreal, QC, Canada; 2Universite de Montreal, Montreal, QC, Canada; 3Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; 4Hopital du Sacre-Coeur de Montreal Centre de Recherche, Montreal, QC, Canada; 5McGill University Health Centre, Montreal, QC, Canada; 6CHU de Quebec-Universite Laval, Quebec, QC, Canada.

Background: In Canada, Quebec province was the most severely hit region during the first year of the SARS-CoV-2 pandemic. We aimed to compare characteristics and outcomes of dialysis patients during the first and second SARS-CoV-2 transmission surges in this province.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
COVID-19 Outcomes in Hospitalized Patients with CKD

Varsha V. Suresh,1 Kay T. Khine,1 Saif M. Borgan,1 Francheska Castro,1 Hiren Patel,1 Abdo Astmar.1 University of Central Florida, Orlando, FL; 2Cleveland Clinic, Cleveland, OH; 3Saint Louis University, Saint Louis, MO

Background: Current research revolving around Coronavirus Disease 2019 (COVID-19) has identified that patients with co-morbid illnesses are at risk for worse outcomes.

Methods: This is a retrospective study comprising an observational dataset of 149 hospitals that included hospitalized patients (n=9366) aged 18 and above with a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Polymerase Chain Reaction (PCR) positive result between January 1, 2020 and May 29th, 2020. Main outcomes and measures included hospital length of stay, Intensive Care Unit (ICU) admission, ventilator dependency, development of acute kidney injury (AKI) and in-hospital death. Baseline patient characteristics were recorded, including demographic variables and comorbidities. Results: A total of 9,366 patients were included in the analysis, of which 4765 (48.5%) had COVID-19. Among the cohort, 61% were Black (including 50% AKI, 82% ESKD-D, and 57% AKI). Overall, 35% required mechanical ventilation, with highest use in the AKI group (54%). 48% of AKI patients required renal replacement therapy (RRT) and 9% treated with ECMO. Mechanical ventilation was lower among KTx recipients (12%) and 9% required RRT. The most common medical treatment was dexamethasone (48%). Mortality was 46% in the AKI and 23% in CKD5-D groups, but 2% among KTx recipients.

Conclusions: We observed high mortality associated with COVID-19 among hospitalized patients with kidney disease, especially in those with AKI. Public health and therapeutic studies should focus on mitigating COVID-19 disease transmission and optimizing outcomes in this vulnerable population.

PO0056
COVID-19 Among Hospitalized Patients with Kidney Disease: Experience at a Midwestern Medical Center
Krista L. Lentine, Seyedmahdi Pahlavani, Yasar Calisakan, Ariel A. Schnell, Nikola E. Marino, Aberdeen X. Taylor, Usama Elewa, Marie D. Philipneri, Amy Mosman, Thanh-Mai N. Vo, Rosemary Ouiphem, Sudhi Annapu, Thomas R. Groll. St. Louis University School of Medicine, Saint Louis, MO

Background: Manifestations of novel coronavirus disease-2019 (COVID-19) range from minimal symptoms to organ failure and death. Preliminary studies suggest that acute kidney injury (AKI) is a common complication of COVID-19 and may predict adverse outcomes. Patients with chronic kidney diseases may be vulnerable to increased risk of serious COVID-19-related complications.

Methods: In this ongoing retrospective cohort study, we examined the characteristics, presentations, treatments, and outcomes of COVID-19 among hospitalized patients with AKI, dialysis-dependent end-stage kidney disease (ESKD-D) or kidney transplantation (KTX) at an urban, Midwestern tertiary center (3/19/2021–3/25/2021).

Results: Among 184 patients, 91 had AKI (49%), 51 CKD5-D (28%), and 42 patients were KTX recipients (23%). Monthly cases ranged from 6 in March to 35 patients in December 2020. Among the cohort, 61% were Black (including 50% AKI, 82% ESKD-D, and 57% KTX). Overall, 35% required mechanical ventilation, with highest use in the AKI group (54%). 48% of AKI patients required renal replacement therapy (RRT) and 9% treated with ECMO. Mechanical ventilation was lower among KTX recipients (12%) and 9% required RRT. The most common medical treatment was dexamethasone (48%). Mortality was 46% in the AKI and 23% in CKD5-D groups, but 2% among KTX recipients.

Conclusions: Dialysis patients with SARS-CoV-2 infections had more favorable clinical outcomes during the 2nd wave, which is consistent with observations in the general population and may be related to improved clinical care.
PO0057

Decision-Making During Uncertain Times: A Qualitative Study of Kidney Patients, Care Partners, and Nephrologists During the COVID-19 Pandemic

Thalia Porteney,1 Susan Koch-Weser,2 Dena E. Ritkin,1 Tamara Isakova,3 Elisa J. Gordon,4 John B. Wong,1 Ana P. Rossi,1 Daniel E. Weiner,1 Ketan Shah,1 DART Invitational, Tufts University School of Medicine, Boston, MA; 2University of California San Diego, La Jolla, CA; 3Piedmont Healthcare Inc, Atlanta, GA; 4Tufts Medical Center, Boston, MA; 5Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Older adults faced treatment decisions for kidney failure during the COVID-pandemic, despite high risk of hospitalization, intensive care, and death. Given heightened uncertainty, clinicians needed to adapt communication about risks, benefits, and treatment decisions during the COVID-19 pandemic. Understanding how to support decision-making during uncertain times can guide clinicians in future public health crises.

Methods: Qualitative study using semi-structured interviews (August-December 2020) with CKD stage 4-5 patients, age 70+, carepartners, and clinicians in Boston, Portland, Maine, San Diego, and Chicago. Thematic analyses were conducted.

Results: Among 76 participants (39 patients, 17 carepartners, 20 clinicians) 13 patients (33%) identified as Black, and 7 (18%) were receiving dialysis. Four themes characterized treatment decision-making during the COVID-19 pandemic: Difficulty communicating risk: balancing hope with caution; Clinicians’ increased support for home dialysis; Patient confidence in chosen modality; and Coping with uncertainty and isolation in CKD. Clinicians struggled to balance discussion of COVID-19 risks while preserving hope. Black patients reported fewer conversations about COVID-19 risks than White patients and had more unaddressed questions. Clinicians reported being more open to home dialysis than pre-COVID-19. While some patients expressed interest in conservative management, few clinicians offered conservative management as an option. All patients who had initiated treatment prior to COVID-19, irrespective of modality, believed that their treatment was safest and optimal during the pandemic. With few clinical conversations incorporating COVID-19-specific risks, patients and carepartners struggled to cope, finding both in-person and telehealth visits safe but isolating.

Conclusions: Although clinicians struggled communicating about COVID-19 leaving patients with unaddressed concerns, patients across modalities felt safe and confident in their treatment. Clinicians developed an openness to home dialysis, though few offered conservative management despite patient preferences. Research should examine optimal approaches to enhance communication and shared-decision making to prepare for future systemic challenges.

Funding: Private Foundation Support

PO0058

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and ESKD

Jackson Heilbronn, Amir Abdi Pour, Giv Heidari-Bateni, Lida Gharibvand, Kwarne B. Aygeman, Sahib D. Grewal, Mohammad Sharif, Sergio Infante, Mita Zahra E. Co, Sayna Norouzi. Loma Linda Medical Center Loma Linda University, Loma Linda, CA.

Background: End Stage Kidney Disease (ESRD) has been shown to be a risk factor for poor outcomes in the setting of COVID-19 infection. Our study aims to identify risk factors for mortality in ESRD patients hospitalized with COVID-19.

Methods: We conducted a retrospective analysis from March 1st, 2020 to January 31st, 2021 at Loma Linda University Medical Center. Inclusion criteria included patients admitted with diagnosis of COVID-19 and history of ESRD prior to admission. Risk factors for hospital mortality were identified with univariate and multivariate logistic regression methods.

Results: A total of 92 patients (age 59.9±13.7) were included in the analysis, of which 88 (28%) were deceased. Multivariable regression analysis (Figure 1) demonstrated that age greater than 70 had adjusted odds ratio (OR) with 95% confidence interval (CI) for mortality 1.10 (95% CI: 1.01, 1.20, p=0.03). An Ejection Fraction of less than 50% had OR=0.63 (95% CI: 0.01, 2.62, 28.77, P= 0.02), adjusted fraction less than 50% OR=1.08 (95% CI: 1.29-27.9, P=0.02), and ferritin >300 ng/ml OR=0.01 (95% CI: 1.01-1.03, P= 0.04) were associated with increased risk of hospital mortality. Adjusted multivariate analysis demonstrated that only ejection fraction less than 50% was associated with increased risk of mortality (OR 9.9, 95% CI: 2.2-45.1, P <0.01)

Conclusions: Age, elevated D-dimer, elevated ferritin and heart failure with reduced ejection fraction were identified as risk factors for hospital mortality of ESRD patients with COVID-19 infection.

PO0059

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and AKI

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Background: Coronavirus disease- 2019 (COVID-19) has the highest mortality in patients with advanced age and those with pre-existing chronic medical conditions. Limited data, however, is available with regard to COVID-19 mortality in acute kidney injury (AKI). We aimed to identify risk factors associated with mortality in patients hospitalized for COVID-19 with AKI.

Methods: This is a retrospective cohort study conducted at Loma Linda University Medical Center (LLUMC) from March 1st, 2020 to January 31st, 2021. Inclusion criteria included patients admitted to LLUMC with diagnosis of COVID-19 and AKI during the admission based on the Risk Injury Failure Loss ESRD (RIFLE) criteria. Univariable and multivariable logistic regression models were utilized to explore risk factors associated with in-hospital mortality.

Results: A total of 320 patients (age 66.5 ±14.4) were included in the analysis, of which 88 (28%) were deceased. Multivariable regression analysis (Figure 1) demonstrated that age greater than 70 had adjusted odds ratio (OR) with 95% confidence interval (CI) for mortality 1.10 (95% CI: 1.01, 1.20, p=0.03). An Ejection Fraction of less than 50% had OR=1.13 (95% CI: 1.03, 1.23, p=0.01), AKI-injury stage had OR=1.25 (95% CI: 1.14, 1.37, p=0.001), positive D-dimer levels had OR=1.18 (95% CI: 1.07, 1.30, p=0.001) and diabetes had OR=1.12 (95% CI: 1.03, 1.22, p=0.01), all significant risk factors for mortality. In addition, Hispanics had a higher risk of mortality with OR=1.20 (95% CI 1.09, 1.33, p=0.001) when compared to Caucasians.

Conclusions: Diabetes, age greater than 70, Hispanic background, Heart failure with reduced ejection fraction, AKI-injury stage, and positive D-dimer level are identified as risk factors associated with higher mortality amongst patient admitted with COVID-19 and AKI.
PO0060
Outcomes of COVID-19 Infection in Dialysis vs. Kidney Transplant Patients: A Nationwide Cohort Study from Qatar

Background: COVID-19 infection carries a high burden and poor outcomes in patients who are immunocompromised like kidney transplant or on dialysis. Our study aim is to compare outcomes between dialysis and kidney transplant patients infected with COVID-19 in the State of Qatar.

Methods: Retrospective cohort study reviewing medical, laboratory and radiographic data of all dialysis and kidney transplant recipients’ patients in our national registry (between February and August 2020). Data collected from a national-based electronic medical record.

Results: 76 patients on dialysis patients had COVID19 vs 43 kidney transplants (p<0.001). Kidney transplant patients with COVID19 tended to be younger than dialysis patients (52 vs. 58 years old, p=0.007), has less hypertension and more history of deep venous thrombosis. Clinical presentation did not differ between both groups with more asymptomatic in dialysis patients compared to kidney transplant patients (14.5% versus 2.3%, p<0.03). More patients died from COVID19 in the dialysis patients vs. kidney transplant patients (11(14.5%) vs. only 1 (2.3%), p=0.034). Inflammatory markers were significantly higher in dialysis patients (IL6 peak and Ferritin) compared to kidney transplant patients.

Conclusions: Our national study showed similar incidence and severity of COVID19 in dialysis compared to kidney transplant in Qatar. Mortality and inflammatory markers were higher in dialysis patients.

PO0062
Mortality in COVID-19 Patients with CKD with and Without Kidney Replacement Therapy in Western Mexico

Background: COVID-19 is a new disease of pandemic proportions. Currently, there are no reports on clinical outcomes in patients with CKD with and without KRT in the Mexican population. Our aim was to describe the clinical outcomes in patients with CKD.

Methods: Retrospective cohort study of hospitalized adult patients COVID-19 confirmed with RT-PCR, from April to December 2020 in a second-level hospital in Western Mexico. Information was obtained from medical records.

Results: 1012 patients were included, of which 130 patients (12.8%) had CKD (65.3% men), with a mean age of 53.8 years, 43.8% with Diabetes Mellitus and 82.3% with Hypertension. 84 patients (64.6%) were on KRT, within which 47 patients were on hemodialysis, 31 on peritoneal dialysis and 6 with a kidney transplant. 46 patients had no KRT, in stages ranging from KDIGO 3b to 5. 78.4% (14 patients (10.7%) required mechanical ventilation. In our study, mortality among patients with normal kidney function was 30.6%. Regarding patients with CKD, patients on hemodialysis had a mortality of 25.5% (OR 0.74, 95% CI 0.39-1.5), patients on peritoneal dialysis had a mortality of 54.8% (OR 2.75, 95% CI 1.35-5.66), patients with CKD and no KRT had a mortality of 43.5% (OR 1.74, 95% CI 1.15-3.17).

Conclusions: In our population, an increased mortality was found in patients with CKD with and without KRT, highlighting the mortality of patients on PD.

PO0061
One-Year Experience of COVID-19 Disease of 700 Chronic Dialysis Patients from Ecuadorian Highlands

Background: In December 2019, first Covid-19 disease cases were reported. The pandemic spread with 114,217,365 cases and 2,533,014 deaths worldwide in March 2021, with 286,155 cases and 15,811 deaths in Ecuador. The aim of this work was to share COVID-19 disease impact on 700 chronic dialysis patients from Ecuadorian highlands, which represents almost 7% of Ecuadorian dialysis population, after one year of pandemic.

Methods: Observational-prospective-multicenter study on 700 Latin American chronic dialysis patients of five different cities from Ecuadorian highlands. Patients were followed since February first, 2020 until 31 January 2021. Patients with COVID-19 symptoms were identified and diagnosis was made exclusively with positive nasopharyngeal swabs PCR testing. Oxygen saturation below 90% at presentation (LOS) classified disease presentation as severe, moderate if symptoms without LOS and asymptomatic if no symptoms. Hospital-stay, time until negative PCR, mortality and laboratory findings were collected.

Results: A total of 205 patients (29%) presented COVID-19 symptoms; 115 tested positive (16%), 60% were men (p=0.03), 25 subjects died (22%). Mortality was related with age above 64 years old, saturation < 90%, severe disease (p=0.03), previous pulmonary pathology and hospitalization (p=0.01). Hospitalization was needed in 74 patients (64%) with hospital stay 11 days (4-15), days until death during hospitalization of 12 days (4-19) and time until negative PCR 20 days (10-25). Symptomatic time was 16 days (11-26).

Conclusions: COVID-19 disease was more frequent in men and has added up to 22% of extra mortality to chronic dialysis population. Patients older than 64 years old, previous pulmonary pathology, LOS at presentation are at higher risk of mortality. Health care burden due to COVID-19 is high in dialysis population suggesting that vaccination program must include dialysis patients and staff involved in their care to diminish mortality, infections and health care burden.
P00063

African Americans Have Lower COVID-19 Mortality Risk Than Caucasians in CKD

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Background: In the general population, African Americans have increased mortality risk from COVID-19. However, this has not been well studied in CKD population.

Methods: We analyzed a national Veteran cohort using data from the VA COVID-19 Shared Data Resource for COVID-positive patients (N=196,269) from 3/1/2020 - 3/9/2021. Diagnosis of COVID-19 was defined as a confirmed positive laboratory test result within 14 days of the date of first positive COVID-19 test or the first negative test for patients who never tested positive for COVID-19. Baseline eGFR was defined as at least one outpatient serum creatinine measurement obtained within two years before the index date or the average of the two closest serum creatinine measurements obtained within two years before the index date. We identified 58,743 patients with valid eGFR measurements. Of this cohort, 51,002 were African American or Caucasian. Mortality data were available for 50,830 patients. We used Cox regression models to compare COVID-19 mortality in African Americans versus Caucasians based on pre-COVID eGFR stratification.

Results: Of the COVID-positive patients with available eGFR and mortality data, baseline mean age was 60 ± 17 years, 24% African American, 76% Caucasian, and 21% with eGFR <60. There were 627 deaths among African Americans and 2,480 deaths among Caucasians. Average follow-up duration was 0.5 ± 0.3 years in African Americans and 0.4 ± 0.2 years in Caucasians. While there was no difference in mortality risk between African American and Caucasian Veterans without CKD, African Americans had lower mortality risk when compared to Caucasians in the CKD subgroup (Table 1).

Conclusions: In the CKD subgroup, African Americans have lower COVID-19 mortality risk than Caucasians. The reasons for this observation are unclear.

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

Table 1. Risk of Mortality in African Americans versus Caucasians in COVID-19 by eGFR Groups

<table>
<thead>
<tr>
<th>eGFR Group</th>
<th>Percent African American</th>
<th>Percent Caucasian</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;60</td>
<td>24%</td>
<td>76%</td>
<td>1.00</td>
</tr>
<tr>
<td>eGFR 60-89</td>
<td>12%</td>
<td>88%</td>
<td>0.90 (0.89, 1.00)</td>
</tr>
<tr>
<td>eGFR 90-119</td>
<td>2%</td>
<td>98%</td>
<td>0.87 (0.84, 0.91)</td>
</tr>
<tr>
<td>eGFR ≥120</td>
<td>0%</td>
<td>100%</td>
<td>0.78 (0.69, 0.89)</td>
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</tbody>
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P00064

COVID-19 Among a Population of Predominantly American Indian and Hispanic American Kidney Transplant Recipients

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Background: COVID-19 leads to higher mortality among organ transplant recipients when compared to the general population.

Methods: In this study, 52 renal transplant recipients with COVID-19 were followed through 90 days from the date of initial diagnosis. We analyzed basic demographics, therapeutics used, and clinical outcomes among patients who survived and those who did not.

Results: Of the entire cohort, 53.8% were Hispanic Whites, 38.5% American Indian, and 5.8% were non-Hispanic Whites. However, 48% required hospital admission and 17% died, with 15% of deaths attributed to complications secondary to COVID-19. All those who died were either American Indian or Hispanic. Comorbidities among the non-survivors included hypertension (100%), chronic kidney disease (67%), diabetes (78%), and either being overweight or obese (100%). 89% had acute kidney injury and 56% required renal replacement therapy. Gender, blood type, and panel reactive antibody prior to transplant did not correlate with disease severity. There was no improvement in mortality during the fall/winter surge compared to the spring/summer surge, though therapies improved during the pandemic. None of the patients who received monoclonal antibody progressed to severe disease or died.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PO0065

Prospective Study of COVID-19 in Patients Receiving Dialysis in Alberta Kidney Care South

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Background: People with kidney failure who are on facility-based hemodialysis (FBHD) are at high risk for COVID-19 infection due to inherent alterations in their immune system as well as the requirement to travel to a health care facility multiple times per week. In Alberta Kidney Care South, AKCS, public health measures and standardized screening of all patients entering clinics and HD units was initiated in March 2020 with COVID-19 testing of all patients who presented with a temperature, COVID related symptoms or a history of exposure to COVID-19.

Methods: All COVID-19 test results performed for AKCS patients are tracked in the electronic kidney database. We performed a 14-month prospective observational study (March 2020 to May 2021) to determine the incidence of confirmed COVID-19 infections, the prevalence of symptoms amongst COVID+ patients and outcomes of hospitalization and death for FBHD, home hemodialysis (HHD) and peritoneal dialysis (PD) patients within the Alberta Kidney Care South program.

Results: We report on our preliminary results up to December 31, 2020. From a population of 1,329 patients, (931 FBHD, 102 HHD and 296 PD) 463 (5.5%) patients were COVID positive. COVID-19 prevalence was 3.5% in FBHD (33/931), 4.4% in PD (13/296) and no HHD patients. The mean age of the cohort was 61 ± 16.5 years with 14.30% female and comorbidities of hypertension 43(93%), diabetes 35(76%), coronary artery disease 16(35%) and heart failure 16(22%). COVID-19 testing was done for the following reasons: contact with a COVID-19 patient in 4(6.7%), resident of a long-term care facility in 3(6.5%) and for symptoms in 31(67%). The most common symptoms were fever (defined as T> 37.3°C with 20(34%), cough 10(20%) and sore throat 6(13%). Overall, 14 patients (30%) were admitted to hospital, 4 of whom went to the ICU and 5(11%) died. There were no differences in hospitalization between FBHD and PD (30% vs 31% respectively p=0.971), ICU admissions (12% vs 0%, p=0.189) or death (12% vs 8 %, p=0.664).

Conclusions: The prevalence of COVID-19 amongst FBHD and PD patients was similar to the general population but with higher rates of hospitalization, ICU admissions and death. People on HHD appear to have very low rates of COVID-19 as compared to either PD or FBHD.
PO0066
Patients on Chronic Maintenance Hemodialysis with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Mortality
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Background: The COVID-19 pandemic has impacted nearly all aspects of the care of patients, particularly those with chronic conditions. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in demographic characteristics in patients with end stage kidney disease (ESKD) who were started on hemodialysis (HD) in 2020 and contracted COVID-19, with those who remained free of the infection in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federate medical records network, to identify 7405 unique adult patients ≥ 18 years from 37 healthcare organizations (HCOs), mostly in the United States, for whom maintenance HD was initiated for ESKD between 1/1/2020 and 12/31/2020 (study period). From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection during the study period. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality in the first three months of initiation of HD for the COVID group.

Results: 903 patients (from 33 HCOs) had a confirmed diagnosis of COVID-19 infection. Patients in the COVID-positive group were less likely to be white (p=0.019), and more likely to: —be of Hispanic/Latino ethnicity (p<0.0001), —have a previously failed kidney transplant (p<0.0001) —have diabetes mellitus (DM) (>90.001), and —have a BMI above 31 (p=0.003). A total of 628 patients died during the study period. After propensity matching, COVID exposure was associated with higher odds of mortality (OR: 2.32; CI: 1.16, 3.24). The survival probability at the end of 3 months was 84.4% for the COVID group, compared with 92.5% for the no-COVID group (p<0.0001).

Conclusions: During the study period, among the patients who were started on HD for ESKD, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, less likely to be white, more likely to have a previously failed kidney transplant, more likely to have DM, and to have a BMI above 31. The COVID-positive group also had higher mortality and a lesser 3-month survival probability compared to the control group.

PO0067
Kidney Transplant Patients with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Outcomes
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Background: The COVID-19 pandemic has been associated with enormous impact on morbidity and mortality, particularly among individuals with chronic conditions and among patients on chronic immunosuppressive therapy. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in kidney transplant (KT) rejection, kidney transplant failure and mortality in patients who received a KT in 2020 and contracted COVID-19 with those who remained free of the infection, in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federate medical records network, to identify 3773 unique adult patients ≥ 18 years, who had received a kidney transplant (KT) between 1/1/2020 and 12/31/2020 at 34 healthcare organizations (HCOs), mainly in the United States. From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection after KT. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality, KT rejection, and KT failure in the two groups during the first 3 months after KT (study period).

Results: A total of 590 patients from 27 HCOs had a confirmed diagnosis of COVID-19 infection. Patients in the COVID group were more likely to be of Hispanic/Latino ethnicity (P < 0.0001). A total of 78 patients died during the study period. After propensity matching, COVID-19 exposure was associated with a higher odds of 3-month mortality (OR: 3.22; CI: 1.56, 6.62). The survival probability at the end of 3 months was 94.4% for the COVID group compared with 98.6% for the no COVID group (p<0.0001). There was no statistically significant difference between the two groups regarding KT rejection during the study period.

Conclusions: During the study period, among the patients who received kidney transplant in 2020, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, had higher mortality, were more likely to have KT failure and have less survival probability. There was no statistically significant difference between the two groups regarding KT rejection.
The Role of Hypertension in Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans
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Background: The discovery that ACE2 was a co-receptor of COVID-19 as well as early clinical findings induced interest in the role of hypertension (HTN) and its treatment with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) with regard to COVID-19 incidence and morbidity. We examined the effect of demographic and common risk factors of HTN and treatment with ACEI, ARBs, calcium channel blockers (CCB) and beta blockers (BB) in patients with COVID-19.

Methods: The VA COVID-19 data resource combines hospital data, administrative and clinical record search results. The prevalence of HTN was defined by its presence in the last 2 years prior to COVID-19 testing. New event (incidence) was determined as occurrence within 60 days thereafter. ACEI and ARB, and CCB and BB were combined, basic demographic and risk factors were categorized for comparisons. Data sets were propensity matched, statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: Of 1,305,466 veterans, we found positive tests (18.1%), HTN (56.9%), ACE or ARB (33.7%), and CCB or BB (15.4%). HTN and treatment had no effect on COVID-19 incidence (OR HTN 1.08, ACE/ARB 1.01, CCB/BB 0.94). Male, white patients aged over 60 years predominated, Age, race, and smoking had no effect on incidence, but DM2 (OR 1.2) and higher BMI (OR 1.4) did. We then examined demographics and risk factors in the high prevalence positive population. Male gender (5.4), age > 60 years (7.5), race non-white (1.6), BMI >30 (2), smoker (2.8), and DM2 (11.8). In these, the most affected outcomes (OR) such as all-cause mortality (7.9), admissions (2.1), ICU admissions (2.5) and ventilator use (2.7) with the exception of BMI which was associated with improved outcomes (0.6). ACE or ARB had no effect (OR 1) while CCB or BB had a small effect (1.26) on outcome.

Conclusions: In conclusion, HTN and anti-hypertensive treatment had no effect on COVID-19 incidence. HTN is associated with age, race, smoking and a diagnosis of DM2. Treatment with ACE or ARB has no effect on morbidity while CCB or BB had a small effect that deserves further evaluation.

Funding: Veterans Affairs Support

Prevalence and Outcomes Associated with Hyperuricemia in Hospitalized Patients with COVID-19
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Background: COVID-19 can increase catabolism and result in hyperuricemia. Uric acid (UA) potentially causes kidney damage by alteration of renal autoregulation, inhibition of endothelial cell proliferation, cell apoptosis, activation of the pro-inflammatory cascade, and crystal deposition. Hyperuricemia in patients with COVID-19 may contribute to acute kidney injury and poor outcomes.

Methods: We included 834 patients with COVID-19 who were >18 years old and hospitalized for >24 hours in the Mount Sinai Health System and had at least one measurement of serum UA. We examined the association between the first serum UA level and major adverse kidney events (MAKE, defined by a composite of all-cause in-hospital mortality or RRT or 100% increase in serum creatinine from baseline), as well as markers of inflammation and cardiac injury.

Results: Among the 834 patients, the median age was 66 years, 42% were women, and the median first UA was 5.9 mg/dL (IQR 4.5-8.8). Overall, 52% experienced MAKE, and 32% died during hospitalization. After adjusting for demographics, comorbidities, and laboratory values, a doubling in serum UA was associated with increased MAKE (OR 2.5 per doubling, 95% CI 1.7-3.5) and in-hospital mortality (OR 1.7 per doubling, 95% CI 1.3-2.3) (Figure A & B). Serum UA levels were independently associated with a higher level of procalcitonin (β 0.6, SE 0.2) and troponin (β 1.2, SE 0.2) but was not associated with the serum ferritin, CRP or IL-6 (Figure C).

Conclusions: In patients admitted to the hospital for COVID-19, higher UA levels were independently associated with MAKE and mortality in a dose-dependent manner. In addition, hyperuricemia was associated with higher procalcitonin and troponin levels.

Funding: Commercial Support - XORTX Therapeutics Inc.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Association of Sodium Abnormalities with Outcomes in Hospitalized Patients with and Without COVID-19
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Background: Several reports of serum sodium (Na) abnormalities have been reported in patients hospitalized with COVID-19. However, the association of Na abnormalities with hospital outcomes have not been well-described in patients with COVID-19 (C19+ v. especially in comparison to those who tested negative (C19-).

Methods: This is a retrospective analysis of the first surge of COVID-19 (C-19) in patients who presented to our ED from December 2019 - June 2020, with a systemic viral illness. There were 5,289 patients from the Covid-19 data set, 1,703 COVID+ patients and 3,586 Covid- patients. Based on a nasal swab PCR patients were divided into two groups: C19 + and C19 -. Na levels at the time of hospitalization were used to divide patients into three groups: hyponatremia (hypon) (<135), normonatremia (normoN) (135-145) and hypernatremia (hyperN) (>145). In C-19 patients, hypon and hyperN were compared to normoN using multivariable (MV) models adjusting for comorbidities to calculate odds/ risk (OR) ratios for outcomes.

Results: C19 + patients, had significant increased incidence of Hypon (26.7% vs 16.2%); and HyperN (4.2% vs 1.3%) compared to C19 - (Figure 1). Non MV analysis, among C19 + patients, found both Hypon and HyperN were significantly associated with mortality compared to normoN. HypoN (compared to normoN) was also associated with higher admission rate to the ICU, acute respiratory distress syndrome (ARDS), and intubation (Figure 2a; 2b)

Conclusions: Among patients admitted with acute viral illness, Na abnormalities on admission were more prevalent in patients with COVID-19 + compared to those who tested negative. COVID-19 + patients with abnormal admission Na concentrations had increased mortality when compared to C - patients. Covid + patients had increased morbidity measured by admission to the ICU, need for intubation, and ARDS. Abnormalities in sodium metabolism predicts a poorer result in Covid-19 care.

Funding: Private Foundation Support

Association of Obesity with 3-Month COVID-19-Related Mortality in ESKD Patients
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Background: In the general population obesity is associated with increased risk of mortality. However, in ESKD patients obesity is associated with lower risk of mortality, particularly in dialysis patients (i.e. the obesity paradox). In COVID-19 patients, obesity exhibits a similar association with mortality as observed in the non-COVID-19 general population. Given the obesity paradox, we questioned the association of obesity with mortality in ESKD patients with COVID-19.

Methods: Data from the European Renal Association COVID-19 Database (ERACODA) were analysed. Association of BMI (kg/m²), divided into: <18.5 (lean), 18.5-24.9 (normal weight), 25-29.9 (overweight), 30-34.9 (obese I) and ≥35 (obese II), with 3-month mortality was investigated using Cox proportional-hazards regression. Results were investigated for the total population and, dialysis patients and kidney transplant recipients separately.

Results: In 3160 ESKD patients (mean age: 65 years, male: 61%), 99 patients were lean, 1151 normal weight (reference group), 1160 overweight, 525 obese I and 225 obese II. During follow-up of 3 months, 28%, 20%, 21%, 23% and 27% of patients died in the lean, normal weight, overweight, obese I and obese II category, respectively. In fully adjusted model, the HRs for 3-month mortality were 1.65 (95% CI: 1.10, 2.47), 1.07 (95% CI: 0.89, 1.28), 1.17 (95% CI: 0.93, 1.46) and 1.71 (95% CI: 1.27, 2.30) in lean, overweight, obese I and obese II vs normal weight patients (Figure). Results were similar among dialysis patients and transplant recipients (p-interaction=0.99).

Conclusions: In ESKD patients with COVID-19, dialysis patients or kidney transplant recipients, obesity is associated with an increased risk of mortality at 3 months. This is contrary to obesity paradox generally observed in dialysis patients. There is need to investigate why in dialysis patients with COVID-19 the survival benefit of obesity is lost.

Funding: Commercial Support - Baxter, Sandoc, Private Foundation Support

Prevalence and Association of Dysnatremia with Outcomes in Hospitalized COVID-19 Patients
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Background: Studies have reported both hypo and hypernatremia in patients hospitalized with COVID-19. We sought to examine the prevalence and association of dysnatremia with clinical outcomes among hospitalized COVID-19 patients at the Mount Sinai Health System.

Methods: We included 5,712 patients with COVID-19 who were a18 years old and hospitalized for ≥24 hours in the Mount Sinai Health System. Patients with ESKD, who received dialysis within the first 24 hours were excluded. We evaluated the association between serum sodium on admission (first level within 24 hours from admission) and the lowest serum sodium during hospitalization with AKI, IMV requirement, and in-hospital mortality using multivariable logistic regression models.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: The median age of patients was 67 (55-78) years, 57% were male, and median serum creatinine was 1.0 (0.9-1.4) mg/dL. On hospital admission, 6% had moderate/severe hypernatremia (<130 mEq/L), 18% had mild hypernatremia (130-134 mEq/L), and 8% had hypotraemia (>145 mEq/L). After adjustment for demographics, comorbidities, and admission lab values, the adjusted OR for moderate/severe hypernatremia, mild hypernatremia, and hypernatremia on admission, compared to normal serum sodium, for in-hospital mortality were 1.59 (1.16-2.19), 1.42 (1.14-1.76) and 2.91 (2.16-3.93), respectively (Figure 1A). Dysnatremias during hospitalization were also associated with all three outcomes, except IMV requirement was not significantly associated with hypernatremia. (Figure 1B)

Conclusions: Both hypo- and hypernatremia on hospital admission and during hospitalization for COVID-19 were independently associated with AKI, IMV requirement, and in-hospital mortality. It is highly likely that dysnatremias are a marker for severity of illness and not causal for the adverse outcomes in COVID-19.

PO0077
The Role of CKD on Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans
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Background: The Coronavirus disease 2019 (COVID-19) pandemic has greatly impacted the global community. With approximately 15% of the United States (US) population having chronic kidney disease (CKD), it is important to understand how COVID-19 interacts with CKD.

Methods: We used the VA COVID-19 resource data to examine the role of CKD on incidence and morbidity of COVID-19. The database combines standard hospital data, administrative and clinical record search results. CKD is defined in this system as having occurred at any time in the 2 years prior to the COVID-19 test, while new results (incidence) refer to 60 day period after positive test. Patients with chronic kidney failure (CKF2yrs) were excluded. We examined the effect of basic demographics and common risk factors on all-cause mortality, ICU admissions, ventilator use, and dialysis. Statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: The population consisted of 1,305,466 veterans. Of these, 235,857 tested positive (18.1%) and 140,143 (11.4%) had CKD. White, male patients aged over 60 years predominated (60.7%, 81.2%, 53.3%). These demographics had no significant effect on COVID-19 incidence. Hypertension (HTN), diabetes mellitus type 2 (DM2), and smoking were taken as risk factors. These were found to have little effect (OR 0.86 – 1.22) while age, race, and in-hospital mortality. It is highly likely that dysnatremias are a marker for severity of illness and not causal for the adverse outcomes in COVID-19.

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PO0078
Association of the COVID-19 Pandemic with ESKD Incidence
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Background: How the COVID-19 pandemic altered ESKD incidence, dialysis initiation, and preemptive kidney transplantation is unknown.

Methods: Using Centers for Medicare & Medicaid Services data, we investigated the incidence of ESKD, dialysis initiation, and preemptive kidney transplantation by week during the first half of 2020. Using Poisson regression, we compared findings in 2020 to a forecast of 2020, had 2017-2019 historical trends continued, overall and by strata of age and race.

Results: Mean weekly counts of patients with new ESKD are shown in the Figure. Incidence of ESKD dropped dramatically in 2020 compared with the expected incidence, particularly during epidemiologic weeks 15-18 (April; incidence rate ratio [IRR] 0.75, 95% CI 0.73-0.78), before approaching pre-pandemic levels in weeks 23-26 (June; IRR 0.93, 0.90-0.95). Across age groups, the decrease was most pronounced during weeks 15-18 among individuals aged ≥75 years (IRR 0.69, 0.66-0.73, compared with individuals aged 45-64 years, IRR 0.80, 0.77-0.84). In terms of race, the decrease was least notable among non-Hispanic Blacks (IRR 0.85, 0.81-0.89) and Hispanics (IRR 0.73, 0.69-0.78). Dialysis initiation reached a nadir during weeks 15-18 (IRR 0.76, 0.74-0.78), and preemptive kidney transplantation decreased even more strikingly during this period (IRR 0.56, 0.46-0.67).

Conclusions: During the first wave of the COVID-19 pandemic in 2020, the number of patients starting treatment for ESKD fell to a level not observed since 2011. Changes in ESKD incidence and utilization of treatment modalities may reflect differential access to care.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
COVID-19 and CKD: An Overview of Reviews to Inform the World

Background: The World Health organization (WHO) declared COVID-19 as a global pandemic in March of 2020. Many studies have assessed the association between different comorbidities and COVID-19 outcomes. In this overview of reviews, we aim to summarize the association between CKD and different COVID-19 outcomes.

Methods: We performed a systematic search through Embase, PubMed, Epistemonikos, and Cochrane as well as preprint databases from January 1, 2020 to January 5, 2021. After searching systematic reviews, we updated the search by identifying primary studies published after August 2020, which was the date of last search in the reviews. We focused on systematic reviews and large primary studies. We followed the GRADE methodology to assess the certainty in effect estimates. Data was pooled based on random effects model.

Results: We included a total of 69 systematic reviews and 66 primary studies in our overview. We did not identify any systematic reviews that directly report on CKD and the risk of contracting COVID-19. There was no convincing difference in the risk of acquiring COVID-19 infection in patients with and without CKD in primary studies (OR = 1.00, 95% CI 0.76-1.33). CKD is associated with higher risk of COVID-19 related mortality pooled hazard ratio (HR) 1.48 (95% CI 1.33-1.65) and pooled odds ratio (OR) 1.77 (95% CI 1.54-2.02) (moderate certainty), hospitalization pooled risk ratio (RR) 1.63 (95% CI 1.03-2.58) (moderate certainty) and disease severity pooled RR 1.56 (95% CI 1.33-1.86) (moderate certainty). Notably, the risk of COVID-19 attributed hospitalization and mortality were higher in patients with more advanced CKD stage.

Conclusions: Evidence consistently demonstrated an increased risk of mortality, hospitalization, and disease severity in patients with CKD and COVID-19 infection. The results highlight the importance of recognizing patients with CKD as a high-risk group and of prioritizing these patients for COVID-19 prevention strategies including vaccination.

PO0081
Virtual Pediatric Systems: AKI in Pediatric COVID-19 Among North American Intensive Care Units

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Background: There is a dearth of large-scale studies assessing the extent of Acute Kidney Injury (AKI) in pediatric COVID-19 patients. We aim to identify the epidemiology and associated risk factors of AKI in the pediatric COVID population through the Virtual Pediatric Systems (VPS) database.

Methods: We performed a retrospective analysis on 2,597 COVID-19 pediatric patients (±24 years) in the VPS COVID-19 database including both males and females with a positive status of SARS-CoV-2 infection, ICU admission, and AKI diagnosis for the AKI group using ICD-10 codes. Variables included in the analyses covered demographics, diagnosis, lab order/results, treatment modalities, length of stay, and mortality. Categorical variables were summarized as percentages while continuous variables as medians. We utilized univariate analysis and multivariate linear regression to assess the differences between the patient group with AKI and those without.

Results: An AKI incidence of 10.7% (297/2597) was found within the pediatric cohort. The AKI group had a significantly higher median hospital length of stay (9.1 days vs. 5.1), PM2 and PM3 probability of death (1.2 vs. 0.96 and 0.99 vs. 0.78, respectively), and proportion of mortality (7.5% vs. 1.6%) in comparison to the non-AKI group. Similarly, the AKI group experienced higher rates of interventions in comparison to the non-AKI group such as vascular access (67.0% vs. 29.8%), airway/respiratory support (55.9% vs. 43.8%), renal support (5.4% vs. 0.4%), and cardio-respiratory support (2.9% vs. 0.8%).

Conclusions: AKI is a severe complication of COVID-19 in children and adolescents. Our study suggests a 4.7-fold increase in mortality in the COVID-19 AKI group. Pediatric COVID-19 patients should be monitored for AKI development and necessitate analyses on manifestations of COVID-19 to improve health outcomes.

PO0082

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Background: How the COVID-19 pandemic altered aspects of dialysis initiation, such as eGFR at initiation, selection of peritoneal dialysis (PD), and, in patients initiating hemodialysis (HD), use of a central venous catheter (CVC), is not fully understood.

Methods: We analyzed the most recently updated quarterly USRDS data available. Using Poisson and logistic regression, we studied weekly changes in eGFR at dialysis initiation, use of PD (versus HD), and use of incident CVCs, overall and by strata of race, such as eGFR at initiation, selection of peritoneal dialysis (PD), and, in patients initiating hemodialysis (HD), use of a central venous catheter (CVC), is not fully understood.

Results: Using Poisson and logistic regression, we studied weekly changes in eGFR at dialysis initiation decreased by 0.33 mL/min/1.73 m² in weeks 19-22, compared with historical trends; non-Hispanic Black patients exhibited the largest decrease, at 0.61 mL/min/1.73 m². The odds of initiating dialysis with eGFR <10 mL/min/1.73m² were higher during weeks 19-22 (May; OR 1.14, 1.05-1.17), corresponding to an absolute increase of 2.9%. Although initiation of both HD and PD fell, PD fell less, such that the odds of initiating PD (versus HD) were 24% higher (OR 1.24, 1.14-1.34) in weeks 11-14. Odds of initiating HD with a CVC increased by 30% (OR 1.30, 1.20-1.41) in weeks 15-18, representing an absolute increase of 3.3%.

Conclusions: In the first half of 2020, eGFR at dialysis initiation fell, most prominently in non-Hispanic Blacks. During the initial wave of the pandemic, odds of utilizing PD, compared with HD, increased by nearly 25%, and odds of using a CVC at HD initiation increased by 30%.

Funding: NIDDK Support
P00083
An ISN-DOPPS Survey of the Global Impact of the COVID-19 Pandemic on In-Centre Haemodialysis Services
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Background: Haemodialysis units (HDUs) have had to rapidly adapt practices and policies to safely continue life-sustaining HD services during the COVID-19 pandemic. We aimed to describe the impact of COVID-19 in different parts of the world.

Methods: The Dialysis Outcomes and Practice Patterns Study (DOPPS) and International Society of Nephrology (ISN) collaborated to web-survey individual HDUs. Responses were obtained in three ways: (1) a survey of DOPPS sites in China (May/June 2020), (2) a random sample (20 units if > 40 units/ country; all units if < 40) stratified by region and HDU census (November 2020 – March 2021), and (3) an open invitation via ISN’s membership list and social media (March 2021). Responses were compared between the ten ISN regions.

Results: There were returns from 412 HDUs (46% public sector, 79% urban; 70% adult, 2% paediatric, 28% adult & paediatric) from 78 countries (9% low-, 24% lower-middle-, 28% upper-middle-, 39% high-income).

Conclusions: The COVID-19 pandemic has had a significant impact on dialysis services and staffing worldwide. Differences in uptake of policies and practices across regions have likely been because of variable access to resources to enable implementation of diagnostic testing algorithms and adequate supply of PPE to implement infection prevention and control recommendations. Guidance should be consistent, adaptable to (nearly) all situations and locations, and evidence based. Going forward, the operationalisation of vaccine programs should be incorporated into guidelines. Disruptions to dialysis services should be minimised, and resource provision (including vaccines) prioritised by policymakers and governments in future waves of COVID-19 and pandemics if we are to protect HD patients, staff, and services.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

P00084

Background: The objective of this study was to evaluate the impact of the COVID-19 pandemic to help conceptualize how patient care delivery, pharmaceutical representative interactions, conferences, and dialysis care may evolve.

Methods: Data was conducted between March 20, 2020 - March 31, 2021, providing coverage on the quickly evolving COVID-19 outbreak via online surveys. 50 nephrologists, neurologists, dermatologists, rheumatologists and gastroenterologists participated in each wave (total 250+) for 16 waves of research.

Results: Practice operation dynamics have changed due to the COVID-19 pandemic. Prior to 2020, 80% of practices were offering telemedicine, now nearly all (90%) offer virtual services. This migration has not come without challenges: 36% of physicians would prefer not to do telemedicine due to issues with patient access (60%), technology (53%) and their own reluctance to conduct new patient visits virtually (44%).

The pandemic has created a high burnout among nephrologists compared to other specialties and nearly 20% would reevaluate their career choice if they could go back. Along with patient care, sales representative interactions have declined due to closed-door policies, with 51% of physicians reporting substantially lower or no engagements (virtual or in-person) compared to pre-COVID. Physicians are looking forward to resuming traditional in-person conferences, with 61% of vaccinated physicians planning to attend in-person if the option is available. COVID-19 has also significantly impacted HD patient care, with 66% of nephrologists reporting an outbreak among HD patients and/or staff. However, despite the obvious advantages of home care during the pandemic, only 34% of nephrologists indicated they were more likely to start a patient on a home modality due to the pandemic in March 2021 – versus 30% in March 2020. Despite their hesitancy, 80% of physicians agree the use of telemedicine will continue after the COVID-19 crisis has passed and estimate that ~20% of weekly visits will be virtual.

Conclusions: The pandemic has changed the delivery of patient care, evolving towards a more virtual model where possible – potentially creating physician burn out and interfering with the physician-patient relationship. The focus is now on the “new normal” post-COVID and the ongoing changes that will have on physicians.

P00085
Analysis of the COVID-19 Pandemic in Home and In-Center Dialysis Populations
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Background: While dialysis patients have a high risk of complications from COVID-19, in-center hemodialysis (ICH) patients show lower SARS-CoV-2 reproduction rates when compared to the general population (Cherif, JASN 2021), possibly related to lifestyle and interventions to prevent SARS-CoV-2 spread. Here we expand the research to study the prevalence of COVID-19 in both home (PD/HHD) and ICHD patients.

Methods: We analyzed COVID-19 cases in PD/HHD and ICHD patients from the U.S. Fresenius Kidney Care (FKC) network, from March 1 to November 27, 2020. Patients were tested for SARS-CoV-2 (confirmed by RT-PCR) when showing signs compatible with COVID-19 infection. We passed and estimate that ~20% of weekly visits will be virtual.

Results: We studied 263,223 patients (age 62.8 ± 14.5 years, 57.7% males) receiving dialysis in the FKC network (87.3% ICHD; 12.7% PD/HHD). In the FKC network, 21,175 (8.05%) were infected with SARS-CoV-2. COVID-19 infection was more prevalent among ICHD patients than PD/HHD patients (8.52% vs. 4.49%). Patients with a higher rate of hospitalization, mortality, and SARS-CoV-2 infection were Black (51.4% vs. 45.1% in PD/HHD and 42.2% in ICHD), older (mean age 70.7 ± 13.1 vs. 66.6 ± 14.2 vs. 64.7 ± 13.5), and had a longer time since transplantation (mean 10.5 ± 11.9 vs. 8.8 ± 10.1 vs. 7.6 ± 9.4 years). In the FKC network, 87.3% of ICHD patients and 12.7% of PD/HHD patients were infected.

Conclusions: The pandemic has changed the delivery of patient care, evolving towards a more virtual model where possible – potentially creating physician burn out and interfering with the physician-patient relationship. The focus is now on the "new normal" post-COVID and the ongoing changes that will have on physicians.
PO0086
Perception of COVID-19 Risk Among In-Center Hemodialysis Patients
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Background: Dialysis patients are at high risk for severe complications related to COVID-19. The present study examined perception of risk of COVID-19 and its impact on behavior modification and emotional well-being among in-center hemodialysis (ICH) patients during the recent COVID-19 pandemic.

Methods: In-depth, semi-structured telephone interviews were conducted between May and July 2020 with adult ICHD patients dialyzing at a large dialysis organization (LDO). Responses were analyzed using inductive thematic analysis. The reliability of categories was examined by an independent coder.

Results: A total of 41 LDO patients were interviewed. The median age was 63 years and 54% were female. Satisfactory inter-rater reliability was achieved for all identified themes (kappa = 0.67 - 0.99). The COVID-19 pandemic caused a high level of worry among ICHD study subjects; 78% of those interviewed felt that they are at high risk of COVID-19. Consequently, subjects reported a high level of compliance with appropriate protective behaviors during the pandemic, such as wearing a mask, sheltering at home, social distancing, and frequent handwashing. The perception of the actual likelihood of contracting the virus during a hemodialysis session was relatively low (M = 3.38 on a 0 to 10 risk scale). The pandemic had no impact on self-reported adherence to dialysis treatment schedules, medications, or diet. However, subjects reported dominating emotions of frustration, fear, stress, depression, and anxiety.

Conclusions: The study subjects were aware of the risk of COVID-19 and seemingly increased compliance with protective behaviors as a consequence. It appears that the pandemic had a strong negative impact on the study subjects' emotional well-being and that additional support in this area might be beneficial.
PO0088
Safety and Efficacy of the Anti-COVID-19 Vaccination Practiced During the Hemodialysis Session
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Background: CKD patients represent a population at high risk of mortality from Covid-19. For 3 years, our hospital has been running a complete intradialytic vaccination project (HBV, Hemophylus, Pneumococcus, Influenza) for hemodialysis patients during dialysis treatment. This study aims to evaluate the safety and the serological response of intradialysis anti-Covid19 vaccination.

Methods: 217 hemodialysis patients from 5 centers were vaccinated with Moderna (Fig. 1). Patients with a previous infection received only one dose. 30 patients (4.6%) refused the treatment. The administration took place one hour after the start of the dialysis session, and therefore with the session still in progress. 44 vaccinated patients, with no history of previous Covid-19 infection, out of a total of 80 dialysis patients, were selected on voluntary basis, in our HD-center, to measure and titrate the anti-RBD S1 antibodies of the virus spike antigen 14 days after the second dose.

Results: Of the 217 patients, 64.3% were male, with a mean age of 70 ± 14 years. 19 patients (8.7%) had mild adverse reactions at site of vaccine-inoculation. Neither serious adverse events nor intradialytic complications were recorded. Table 1 shows the characteristics of the 44 patients whose antibody titration was performed. Seroconversion was achieved in 41 patients (93.18%), anti-RBD S1 titer was 936,6 ± 661,7 U/I/mL.

Conclusions: Our preliminary data form our study shows that intradialytic vaccination for Covid-19 is safe and effective and solves logistic problems in prophylaxis’s management. This approach should be preferred in hemodialysis patients. We are planning to extend anti-RBD S1 antibodies monitoring of the Sars-Cov2 virus in all HD Centers involved in the study and to include Peritoneal Dialysis’ patients.

PO0089
Assessing the Impact of a Renal Care Management Program on Disease Progression Prior to and During the COVID-19 Pandemic
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Background: The transition to dialysis among chronic kidney disease (CKD) patients marks a significant change in health accompanied by increases in morbidity and health care costs. Delaying this transition means extending the patient’s quality of life and cost savings. The effects of renal care management on the transition to dialysis and whether having access to the program impacts the risk of transitioning to dialysis as well as the timeline of transitioning to dialysis is necessary to study given the increased role of case management programs with the advent of the COVID-19 pandemic. Understanding the role of disease management programs provide direction for management programs across the globe.

Methods: The design is a retrospective, cohort study of patients in the US drawn from a national claims database who were identified as having CKD 4 or 5 on July 1, 2018. The data was analyzed to determine whether program access affected the rate of transition to dialysis and the likelihood of transitioning to dialysis from 2018 to 2020.

Results: We followed the cohort of 7,992 participants (3,561 with access to Kidney Resource Services and 4,431 without access to Kidney Resource Services) during a two year period from 2018 to 2020. Those with access to Kidney Resource Services transitioned to dialysis later than those without access to the program. Further, after controlling for patient risk and characteristics, patients with access to the program had a 22 percent reduced risk of initiating dialysis compared to those without access.

Conclusions: Patients with stage 4 or 5 CKD who have access to renal care management have a reduced risk of transitioning to dialysis as well as a later transition to dialysis compared to CKD patients without access to renal care management. Further research is needed given the increased need for education during and post the COVID-19 pandemic to address social and clinical determinants of health.

PO0090
Stigma Syndemics and ESKD in Disenfranchised Urban Communities Fighting COVID-19
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Background: Although COVID-19 is impacting all communities, the distribution of its harms is not equal. Poor, urban people of color with compromised health are particularly hard-hit. This study explores how patients with end-stage kidney disease (ESKD), living in underprivileged urban communities, manage their illness and treatment experiences and disease-associated stigmas in the face of COVID-19.

Methods: We used purposive sampling to enroll patients with ESKD at a safety net hospital in Boston, MA. 12 remote ethnographic interviews were conducted from December 2020 to June 2021. Interviews were recorded and transcribed, and data were analyzed using grounded theory and dimensional narrative analysis. We identified dominant themes reflecting the biosocial harms caused by ESKD as well as patients’ sense of isolation and stigmatization before and during the COVID-19 pandemic.

Results: The mean age of patients was 56±14 years, 50% were female, and 90% self-identified as Black. Almost all patients reported adverse effects from dialysis treatment which leaves them depleted and precludes them from working. Facing the biosocial implications of dialysis, patients also experienced severe economic hardship which has been intensified by the COVID-19 pandemic. While many patients framed COVID-19 as “just one more thing” and denied increased stigmatization by others due to their potentially increased susceptibility to infection, male patients more frequently reported experiencing racial stigmatization and narrated it as contributing to and exacerbating their chronic illness and suffering.

Conclusions: Biosocial and environmental factors as well as institutional racism and stigmatization play significant roles in amplifying the burden of ESKD in patients of color who are now syndemically impacted by COVID-19 (Figure 1). A better understanding of
COVID-19: Health Systems and More

**PO0091**

COVID-19 Vaccine Hesitancy and Uptake Amongst a Multiethnic Hemodialysis Population

**Background:** Broad adoption of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is key to fighting the spread of Covid-19. Hemodialysis patients are at increased risk of exposure to SARS-CoV2 and associated with high morbidity and mortality if they contract Covid-19, therefore attaining high vaccination rates in dialysis patients is of utmost importance. The aim of this study was to establish the prevalence of vaccine hesitance across the multi-ethnic population of dialysis patients in North East London, and to assess whether vaccine uptake could be improved by offering vaccination in a familiar setting by trusted healthcare professionals.

**Methods:** Prior to the initiation of the hemodialysis vaccine programme, a survey was conducted of 837 in-centre haemodialysis patients to identify those willing to accept the vaccine. The vaccine was then offered to all haemodialysis patients during their dialysis attendance, by their dialysis team of nurses and nephrologists.

**Results:** Of 674 responses, 476 (71%) patients reported willingness to accept the vaccine. However only 41% of the 232 patients of Black ethnicity stated that they would accept the vaccine with 59% undecided or declined, compared to acceptance of 77% and 82% of the Asian and White patients respectively (p<0.0001). The actual acceptance rate was significantly higher in all ethnic groups than that predicted by the survey (82.2% uptake in total), with 71.5%, 86.0% and 89.3% in Black, Asian and White cohorts respectively (p=0.0001). In total, 59.1% of patients who responded ‘no’ in the initial survey accepted the vaccine when offered on the unit.

**Conclusions:** Though vaccine hesitancy remains a concern, even in this particularly vulnerable patient group, our data show that uptake can be improved by offering Covid-19 vaccination in a familiar environment by a trusted healthcare team.

**PO0092**

Navigating Vaccine Hesitancy in a Hemodialysis Clinic
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**Background:** Pre-vaccination, SARS-CoV2 infected 20% of our hemodialysis clinic patients. Over 60% responded to the survey, 18% said they would decline vaccination due to vaccine hesitancy. Increasing access and hesitancy are significant barriers to vaccination among minority groups. Over 90% of our patients self-report as Black or African American, thus we created a multidisciplinary vaccine navigation program to optimize COVID-19 vaccination.

**Methods:** We surveyed the patients’ vaccination attitudes before the vaccine was available. All care team members: patient care technicians, nurses, social worker, dieticians, and nephrologists were educated to provide the patients with the efficacy and safety of the vaccine. Our affiliate hospital had an mRNA vaccine clinic. Patients were approached and consented to participate in the vaccine navigation program.

**Results:** Over 60% responded to the survey, 18% said they would decline vaccination and 39% were unsure. Figure 1 shows the growth of the percentage of patients receiving one and two doses of the vaccine. The first patient received a dose on 1/9/2021. On 1/28/21, the hospital vaccine clinic invited dialysis patients who used the hospital’s services. On 2/4/21, we provided the hospital a complete list of patients. On 2/11/21, a vaccine hotline was implemented and a renal dietitian became the dialysis clinic’s vaccine navigator scheduling and tracking patients’ vaccine appointments, avoiding conflicts with their dialysis times and coordinating transportation. Nurses documented vaccinations. A spreadsheet was emailed weekly to team members to track vaccinations and to remind patients of vaccine appointments. All of the staff discussed vaccination with patients who were hesitant or declining the vaccine. By 5/4/21, 89% of the patients had received at least one dose, 79% had received two doses.

**Conclusions:** Although many patients had vaccine hesitancy, the growth curves show the rapid adoption of the vaccine. The main barrier to the vaccine was access. Multidisciplinary care in the hemodialysis clinic can facilitate access to care and may be a model for navigating kidney transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

**PO0093**

Disparities in CKD Risks: Data from the CURE-CKD COVID-19 Sub-Registry
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**Background:** The SARS-CoV-2 pandemic accelerated health disparities in chronic kidney disease (CKD). Here, we describe risk factors and access to care surrogates (area deprivation index-ADI) for clinical outcomes among SARS-CoV-2-tested patients in the CURE-CKD Registry.

**Methods:** We performed a COVID-19 Sub-Registry within CURE-CKD (1/1-6/30/2021; N=171,988) of patients with CKD, diabetes (DM),pre-DM, or hypertension (HTN) with SARS-CoV-2 testing at UCLA Health (UCLA): N=17,884 and Providence St Joseph Health (PSJH; N=154,104). Statistical analyses and fitted multivariable logistic regression models were adjusted for age and sex. The UCLA cohort included analyses for acute kidney injury (AKI), ADI (for poor housing, education, income), Charlson Comorbidity Index (CCI), and severe COVID-19 disease.

**Results:** Odds ratios (OR) of COVID-19 positivity for the combined UCLA + PSJH population, as well as OR of having severe COVID-19 disease in the UCLA cohort are presented (Table). OR[95%CI] for AKI were higher for ages ≥80 years (1.77[1.14-2.64]), ADI by state (1.12[1.06-1.18]), CKD (12.20[8.46-17.58]) and pre-existing DM (3.65[2.62-5.08]), p<0.001. In the UCLA CURE-CKD population, AKI was associated with severe COVID-19 (r=0.26) and ICU admissions (r=0.29). Mortality was associated with severe COVID-19 disease (r=0.5).

**Conclusions:** Non-White and/or LatinX race/ethnicity, ADI, CKD, DM, and older age were associated with higher risks of COVID-19 positivity, disease severity, and mortality in CURE-CKD. Efforts on viral screening, timely COVID-19 diagnosis, and optimal care delivery for patients with or at-risk for CKD are needed.

**Funding:** Private Foundation Support
PO0094
Beliefs About and Impact of the COVID-19 Pandemic on a Population of Inner City Kidney Transplant Recipients (KTRs)  
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Background: The COVID-19 pandemic was especially stressful for indigent people with multiple health conditions. We examined beliefs and behaviors at the height of the pandemic in a population of inner-city KTRs.

Methods: 40 KTRs followed at our Center were surveyed by telephone including questions about behaviors, knowledge and attitudes regarding COVID-19 using yes/no or Likert scale answers as well as the Stress and Social Support and Health Beliefs Questionnaires.

Results: Mean age was 57±1.8 yrs, with 22 males and 18 females, 27 (77%) Black, (4) White 11% and 8 (23%) other. Time since transplant 7.75±1.0 yrs. 35% (9/26) felt difficulties were piling up so high that they could not overcome them. 13% (4/31) reported it was more difficult to pay for medications and were more likely to skip doses to make them last longer (r=0.473, p=0.008). 75% (23) were afraid of COVID-19. 51% (17/33) were afraid of catching it from a family member, 54% (18) from a friend, 84% (26) limited any in person interactions, 44% (19) avoided leaving home for any reason and 45% (15) avoided going to any public spaces. 5% reported being more afraid of COVID-19 were more likely to report poor health (r=0.39, p=0.032), to report being afraid to leave their home (r=0.48, p=0.006), were more likely to have contacted their provider more than 4-6 times in the past two months (p=0.034), to state that their health was worse since the pandemic (r=0.39, p=0.032), and to say that their condition keeps them from working (r=0.52, p=0.027). They also believed that eating Chinese food could increase COVID-19 risk (r=0.37, p=0.039).

Conclusions: In our population of inner-City KTRs: 1. Two thirds were afraid of COVID-19, including catching it from a friend or family member, and limited leaving their home. 3. They were also more likely to report poor health. contact their healthcare provider multiple times, as well as state their condition made it impossible to work and believe that one could catch COVID-19 from Chinese food. 4. Over 10% were financially stressed and skipped doses of medication to make them last longer and a third felt it difficult to cope overall. 5. Follow up will be necessary as the pandemic subsides to examine if there was a detrimental effect on graft survival due to multiple stressors that could affect adherence in this population.

PO0095
Barriers and Facilitators to Emotional Well-Being and Healthcare Engagement in COVID-19: A Qualitative Study Among Patients with Kidney Disease and Their Caregivers  
Jia Hwei Ng,1 Candice Halinski,2 Devika Nair,2 Michael A. Diefenbach,1 Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, 2Vanderbilt University Department of Medicine, Nashville, TN.

Background: Patients with chronic kidney disease (CKD) have disproportionately faced poor health outcomes during the coronavirus disease-19 (COVID-19) pandemic. Barriers and facilitators to patients’ and caregivers’ emotional well-being and healthcare engagement have not been deeply described, leaving a gap in interventions during future crisis settings.

Methods: We conducted a qualitative study among patients with CKD (stages 4-5), kidney failure, kidney transplantation, and their caregivers. Interviews were guided by Leventhal’s Model of Self-Regulation that emphasized individual interpretations and emotional responses to health threats as determining factors of health behaviors. Interviews were audio-taped, transcribed, and analyzed thematically.

Results: Twenty-eight patients (median age 63, self-reported race: White 57%, Black 18%, Asian 1%, others 14%) and 14 caregivers were interviewed over six months. Barriers and facilitators related to patients’ emotional well-being included 1) negative emotional responses (feelings of increased vulnerability, anxiety, social isolation, and depression); 2) coping behaviors (adaptive coping via self-preservation and emotion regulation; maladaptive coping via alcohol and unhealthy eating); 3) and the need for caregiver support for daily tasks. Barriers and facilitators to healthcare engagement included: 1) continued trust in the medical community (“I put my faith in [my doctor’s] knowledge”); and 2) technology (telehealth was a facilitator to access for some but inadequate for multidisciplinary care “[my] transplant evaluation was stopped…we could not go to the cardiologist”). Caregivers reported higher burden compared to before the pandemic.

Conclusions: Patients and caregivers widely reported negative emotional reactions to enforced pandemic-related social isolation. Coping efforts were partially successful. Telehealth provided adequate access to kidney health services for some but was insufficient for those requiring multidisciplinary care. Lessons learned from the COVID-19 pandemic suggest that patients with kidney disease may benefit from psychosocial and multi-modal structural support to offset social isolation, reduce caregiver burden, and bolster access to multidisciplinary care during future crisis settings.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.

Three-Month Clinical, Functional, and Mental Outcomes in Kidney Transplant Recipients Surviving COVID-19  
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Background: Kidney transplant patients are at high risk for COVID-19 related mortality. However, limited data are available on longer term clinical, functional and mental outcomes in patients that survive COVID-19.

Methods: Data from adult kidney transplant patients that presented with COVID-19 between February 1st, 2020 and January 31st, 2021 were retrieved from the ERACODA database. Data from patients with complete data for vital status, hospitalization and/or ICU admission was used for this analysis.

Results: 912 patients were included with a mean age of 56.7 (+13.7) years. 26.4% were not hospitalized, 57.5% hospitalized, and 16.1% hospitalized and ICU admitted. Three-months survival was 82.3% overall and 98.8%, 84.2% and 49.0% resp. in each group. Three-months acute rejection, need for dialysis / CVVH at any time point, and graft failure occurred in the overall group in 1.0, 2.6% and 1.8% resp., and in 2.1%, 10.6% and 10.6% of ICU admitted patients resp. Of the surviving patients 83.3% had reached their prior functional status within 3 months. Of patients that had not yet reached their prior functional status, it was expected that 79.6% still would do so within the coming year. 94.4% had reached their prior mental status. Of patients that had not yet reached their prior mental status, it was expected that 80% of patients would do so within the coming year.

Conclusions: In patients alive at three-months follow-up, graft loss was rare, and most patients had reached their pre-COVID-19 functional and mental status.

Table 1

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total</th>
<th>Not hospitalised</th>
<th>Hospitalised, no ICU</th>
<th>Hospitalised, ICU (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, ±SD)</td>
<td>56.7 (±13.7)</td>
<td>31.4</td>
<td>2.9 (±0.2)</td>
<td>1 (±0.5)</td>
</tr>
<tr>
<td>Medical history (CVVH, ±SD)</td>
<td>7.9 (±7.1)</td>
<td>3.7 (±2.3)</td>
<td>2.1 (±0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Graft loss, ±SD</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Readmission (p=COVID-19 in hospital, ±SD)</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Readmission (p=COVID-19 in hospital, ±SD)</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0 (±0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PO0096
Clinical, functional, and mental outcomes in kidney transplant recipients three months after being diagnosed with COVID-19. Data of 487 patients were available for analysis of graft function related outcomes. Data of 450 patients were available for functional and mental status outcomes.
Clinical, Functional, and Mental Outcomes in Hemodialysis Patients 3 Months After COVID-19 Diagnosis

Marc H. Hemmeler,1 Marilyn Noordzij,2 Priya Vart,3 Kitty J. Jager,3 Raphael Duivenvoorden,2 Alfero C. Abrahams,2 David A. Arroyo,3 Yuri Battaglia,4 Robert Ekart,5 Francesca Mallamaci,6 João Oliveira,7 Andrew J. Driscoll,5 Sivkumar V. Lifferth,8 Dr. Casper F. Franssen,1 Luuk Hilbrands,2 Ron T. Gansvoort1 on behalf of the ERACO Collaborators

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Background: There is overwhelming evidence that hemodialysis (HD) patients are at high risk of death in the first month after developing COVID-19. However, less is known about their long-term mortality risk and functional and mental outcome. We aimed to assess their outcomes in a large cohort of HD patients 3 months after COVID-19 diagnosis.

Methods: From ERACO, we included adult HD patients who presented with COVID-19 from February 1, 2020-January 31, 2021 and with complete data on vital status and hospitalization. Recovery of functional and mental status was estimated by the treating nephrologist. Logistic regression was used to calculate odds ratios (OR) with 95% confidence interval (95%CI) for the likelihood of reaching the pre-COVID-19 status.

Results: A total of 2,249 HD patients (mean age 67.5 ± 14.4 years) were included, of whom 1,087 (44%) were not hospitalized, 1,163 (48%) were hospitalized but not admitted to an ICU, and 197 (8%) were hospitalized and ICU-admitted. In these 3 groups, the survival probability at day 28 was 90%, 75% and 47%, and at 3 months 90%, 73% and 40%, respectively. For 854 patients who survived 3 months after COVID-19 diagnosis, data on functional and mental status was available. 743 (87%) reached their pre-COVID-19 functional status within 3 months. 11 patients had not yet reached this, but it was expected that 58% of them would do so within 1 year. Higher age (adjusted OR: 0.97; 95% CI: 0.96-0.99), higher frailty score (0.81; 0.70-0.93) and ICU admission (0.11; 0.05-0.26) were associated with a lower likelihood of reaching the pre-COVID-19 functional status. Pre-COVID-19 mental status was reached by 803 (94%) patients. Higher frailty score (0.76; 0.65-0.89) and ICU admission (0.27; 0.11-0.67) were associated with lower likelihood of reaching prior mental status. For 56% of the 51 patients who had not yet reached their prior status, it was expected that they would do so within the coming year.

Conclusions: Three months after a COVID-19 diagnosis, most HD patients who were not admitted to the ICU were still alive. Furthermore, a vast majority had already reached their pre-COVID-19 functional and mental status at that time point.

Funding: Commercial Support - The ERACO project receives unrestricted grants from Baxter and Sandoz., Private Foundation Support.

Anxiety in Patients with CKD During the COVID-19 Pandemic: Predictors and Consequences Among Chronic Renal Insufficiency Coronavirus (CRIC) Study Participants

Kirsten S. Dorans,1 Julie A. Wright Nunes,2 Douglas E. Schaubel,3 Daohang Sha,4 Mahboob Rahman,4 Harold I. Feldman,5 CRIC Study Investigators 1Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; 2University of Michigan Medical School, Ann Arbor, MI; 3University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4Case Western Reserve University, Cleveland, OH.

Background: Chronic kidney disease (CKD) is associated with anxiety and depression. Though the Coronavirus 2019 (COVID-19) pandemic has increased stressors on patients with CKD, their predictors and consequences, including on virus mitigation behaviors are lacking.

Methods: From June to October 2020, we administered a survey about anxiety related to the COVID-19 pandemic to 1888 participants in CRIC. We examined associations of anxiety with demographics, clinical indices, health literacy, health-related behaviors and COVID-19 mitigation behaviors.

Results: Four anxiety-related constructs were assessed: one composite overall anxiety construct and three sub-constructs: general anxiety, worry, mood/feelings. Construct scores correlated moderately to strongly with each other (0.48-0.81). Construct scores had moderate to strong correlations with each other (0.48–0.89) and with global anxiety construct and three sub-constructs: general anxiety, worry, mood/feelings.

Conclusions: Several factors predict higher anxiety related to the COVID-19 pandemic. Although anxiety is typically thought to be an undesired outcome, in addition to being associated with less healthy behaviors, anxiety was associated with higher self-reported mask wearing. Our study indicates a need for interventions to support healthy behaviors and virus mitigation strategies, without provoking or worsening anxiety in patients with CKD.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

Multivariable-adjusted logistic regression examining associations between overall anxiety composite score and self-reported behaviors. During the pandemic, higher global anxiety scores were associated with higher odds of eating less healthy foods, reduced physical activity, and weight gain as well as reporting always wearing a mask in public in the past week.

Hand Sanitizer Overdose in the Era of COVID-19

Neerakha Mettupalli, Ashton N. Breithaupt, Alice Cheedid. The University of Tennessee Health Science Center College of Medicine, Memphis, TN.

Introduction: Isopropyl alcohol is a common ingredient in hand sanitizers. Ingestion should be suspected if patient presents with high osmolar gap & pseudo renal failure without metabolic acidosis.

Case Description: 44 y/o female with h/o of HTN & hypothyroidism, brought to the ED after altered mental status. 2 bottles of hand sanitizers were found empty next to her. She was drowsy, unable to provide any further history. Vitals T: 36.7 C, HR 91, BP 124/84, RR 14, SaO2 97 on RA. Physical exam was unremarkable. Initial labs on admission: Serum creatinine 2.47, i-stat creatinine at 0.7, bicarb 24, AG 8, serum osmolality 341, osmolar gap of 57. Ethanol level was negative. Table 1 outlines the patient’s labs. Given normal bicarb, normal AG with very high osmolar gap, isopropyl alcohol ingestion was suspected. IV fomepizole was started, as some hand sanitizers contain methanol. Fomepizole was continued until osmolar gap closed. No dialysis was required. Methanol level was undetectable. Acetone level high 176. Isopropanol level high 49. Patient’s mental status improved with supportive measures.

Discussion: Isopropional ingestion presents with normal bicarb, normal AG with very high OG. Treatment is usually supportive. Clinicians should be aware of falsely elevated calcium if measured via colorimetric method due to acetone’s interference. Our case presents a new challenge added to numerous challenges physicians are facing in the COVID Era.

Labs

Federated Learning for AKI Prediction in COVID-19 Patients


Background: Predictive models are trained on single-center data and are non-generalizable, and multi-center data pooling raises privacy concerns. Federated learning (FL) trains models by updating parameters from a central aggregator without sharing raw data. We used FL to predict acute kidney injury (AKI) in COVID-19 patients within 3 (AKI) and 7 (AKI) days of admission as a use case.

Methods: We selected 4035 COVID-19 patients admitted to 5 hospitals in New York City, after excluding patients with AKI, to train logistic regression and logistic regression with L1 regularization (LASSO) models through 3 approaches: local data, pooled data from all sites, and a FL method.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: Federated models outperformed local models as measured by area under the receiver operating characteristic curve (Figure 1, Table 1). SHAP plots indicate differences in feature importance between LASSO models in AKI3 prediction (Figure 2).

Conclusions: FL has utility for developing accurate predictive models without compromising patient data.

Funding: NIDDK Support

Table 1.

<table>
<thead>
<tr>
<th>Model</th>
<th>Cross Site ROC Curve</th>
<th>Cross Site Average</th>
<th>Mean SI Score (AKI3)</th>
<th>Mean SI Score (AKI1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0.706</td>
<td>0.721</td>
<td>0.719</td>
<td>0.721</td>
</tr>
<tr>
<td>Federated</td>
<td>0.777</td>
<td>0.777</td>
<td>0.777</td>
<td>0.777</td>
</tr>
<tr>
<td>Logistic Regression</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
</tr>
<tr>
<td>LASSO</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
</tr>
<tr>
<td>LASSO (Local)</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
</tr>
<tr>
<td>LASSO (Federated)</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
<td>0.622</td>
</tr>
</tbody>
</table>

Case Description: On admission, the patient was afebrile with normal vitals and unremarkable physical examination. He noted his GCA had been in remission off treatment for two years. Labs noted new-onset microscopic hematuria and proteinuria (1.5 g/24 hr) as well as serum creatinine (SCr) of 2.2 mg/dL from 1.4 ten days prior. His sedimentation rate and C-reactive protein were also markedly elevated (119 mm/hr and 105 mg/L). Given rapidly progressive glomerulonephritis and small vessel vasculitis (Figure 1A & 1B), Serologies returned with positive p-ANCA and high-titer myeloperoxidase antibody, confirming the diagnosis of Microscopic polyangiitis (MPA). He was transitioned to oral Prednisone and given the first of two doses of IV Rituximab. One week post-biopsy his SCr was 1.8 mg/dL.

Discussion: Renal involvement by MPA in patients with GCA is rare but has been reported. This case is unique in its temporal relation to COVID-19 vaccination. There have been reports of crescentic IgA nephropathy as well as minimal change disease following COVID-19 vaccination but we are unaware of cases of de novo or recurrent vasculitis. While causality is difficult to prove, clinicians should closely monitor patients post-vaccination.

PO0102

COVID-19 Pandemic Highlights Global Inequities in Chronic Hemodialysis Care: A DOPPS/ISN Survey

Elliott K. Tannor,1 Brian Bieber,2 Dibya Singh Shah,1 Chimota T. Phiri,2 Rhys D. Evans,2 Ryan E. Aylward,9,10 Murilo H. Guedes,2 Ronald L. Pisoni,2 Bruce M. Robinson,2 Fergus Caskey,3 Adrian Liew,4 Valerie A. Luyckx,9,10 Vivekanand Jha,3 Roberto Pecoits-Filho,2 Gavin Dreyer.6 ISN DOPPS collaboration 1Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Tribhuvan University Teaching Hospital, Kathmandu, Nepal; 4Mount Elizabeth Medical Centre, Singapore, Singapore; 5The George Institute for Global Health, New Delhi, India; 6Barts Health NHS Trust, London, United Kingdom; 7Queen Elizabeth Central Hospital, Blantyre, Malawi; 8Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 9University of Bristol, Bristol, United Kingdom; 10University of Cape Town, Rondebosch, South Africa; 11University of Cape Town, Rondebosch, South Africa; 12Brigham and Women’s Hospital, Boston, MA; 13The University of British Columbia, Vancouver, BC, Canada.

Background: Patients receiving chronic hemodialysis (HD) are highly vulnerable in all settings. It is unknown whether the COVID-19 pandemic has disproportionately affected the care of chronic HD patients in low (LIC) and low-middle income (LMIC) settings. This survey aimed to identify global challenges and inequities in HD care delivery during the COVID-19 pandemic.
PO0104
Cutaneous Manifestations of COVID-19 Virus in ESRD Patients
Iritza Hasan, Charles W. Heilig. University of Florida College of Medicine - Jacksonville, Jacksonville, FL.

Introduction: COVID-19 viruses including Pfizer (BNT162b2) & Moderna (mRNA-1273) have been authorized for emergency use by FDA since late 2020. Although there are reported cases of cutaneous manifestation post mRNA COVID vaccines, literature is lacking for the same in patients with ESRD. Here we report two cases of generalized cutaneous manifestations in patients with ESRD.

Case Report 1: A 76-year-old female with DM, HTN, SLE (in remission) & COVID-19 was admitted with bilateral leg edema & generalized skin reaction 2 weeks post receiving 1st dose of Moderna vaccine. Skin manifestations included generalized macular & blistering lesions, painful ruptured vesicles & skin weeping. Skin biopsy revealed epidermal necrosis, neutrophilic spongiosis & negative DIF. The 2nd case was a 54-year-old male with DM & ESRD on PD who was admitted with adenopathy & diffuse post 2nd dose. Pathologically, lesion reported were not considered to be drug reaction. Immunological tests failed to detect an SARS-CoV-2 or antiviral antibody.

Discussion: Both cases recovered fully with education & management of DM & ESRD. Here we report 2 cases of generalized skin manifestations in COVID-19 patients with ESRD, both were non-dialysis dependent & had DM & ESRD on PD. Conclusion: Skin manifestations in COVID-19 patients with ESRD are rare & usually non-specific. Widespread screening for active immunological processes is recommended in case of skin manifestations in COVID-19 patients with ESRD.

PO0105
GloMERULAR DISEASE IN TEMPORAL ASSOCIATION TO SARS-CoV2 RNA VACCINATION: A SERIES OF 16 CASES
Tiffany Caza,1 Christopher P. Larsen,2 Patrick D. Walker,3 Regan M. Seipp,4 Hassan Amin,4 Irina Vancea,2 Mandolin S. Ziadie,2 Nidia C. Messias,2 Clarissa A. Cassol.1 1Arkana Laboratories, Little Rock, AR; 2South Colorado Nephrology Associates, Pueblo, CO; 3DuPage Medical Group, Naperville, IL; 4The Kidney Group of Memphis, Memphis, TN; 5Memorial Regional Hospital, Miramar, FL.

Background: Vaccination is considered safe in patients with chronic kidney disease. However, given the ability to activate the immune system, immunizations carry a risk of inducing inflammatory disease flares. The mass vaccination for SARS-CoV-2 provides a unique opportunity to investigate potential vaccine-associated glomerular diseases. Methods: Kidney biopsies were reviewed in patients who presented with acute kidney injury (AKI) and/or nephritic/nephrotic syndrome within 3 weeks of SARS-CoV-2 vaccination. Results: Sixteen patients with a new onset of kidney disease flare or flare within 3 weeks of SARS-CoV-2 vaccination were identified and had full glomerular disease on biopsy. Eleven patients had two vaccine doses prior to symptom onset. The patient cohort included 16 males and 10 females, with an average age of 58 years. Biopsy diagnoses included IgA nephropathy (n=7), minimal change disease (n=4), ANCA-associated glomerulonephritis (n=3), membranous glomerulopathy (n=1), and diffuse lupus nephritis (n=1). Conclusions: Vaccine-associated glomerular diseases in patients on chronic kidney disease should be considered and further studies are needed to investigate the potential association.
were negative for monoclonal immunoglobulin (Ig) or cell line, amyloid, or malignancy. Though symptoms had long since resolved, she was still PCR-positive for SARS-CoV-2 on nasal swab. Upon discharge she was given cyclophosphamide (Cy). Her renal function improved (Cr 2.5) and she came off HD 2 weeks later. Her outpatient oncologist opted not to continue therapy. However, 2 months later she was readmitted with nausea, dyspepsia, and anasarca with recurrent AKI (Cr 6.7) and nephrotic syndrome. HD was restarted. Repeat kidney biopsy [Figure] was noted to be a “carbon copy” of the first, SPEP, spot UPEP, and sFLC were again negative. She was started on Cy, bortezomib, and Dex with similar partial response (Cr <2.5).

**Discussion:** PGNMID is a rare type of monoclonal gammapathy of renal significance (MGRS) that often has no detectable extrarenal monoclonal Ig or cell line. MGRS and PGNMID, though usually not postinfectious, have been reported with other viruses (e.g., viral hepatitis, parvovirus-B19). However, though causality is unclear, this is the first case of MGRS reported in association with COVID-19.

**Case Description:** Routine labs 1 day prior to COVID-19 mRNA vaccine series were stable with serum creatinine (Cr) 0.8 mg/dL, urine protein creatinine ratio (UPCR) 0.42 mg/mg (65 mg/dL of protein), and serum albumin 4.8 g/dL. Thirty-one days after the second COVID-19 vaccine, routine labs were significant for nephrotic range proteinuria with UPCR >6.21 mg/mg (>2500 mg/dL of protein), hypoalbuninemia (1.7 g/dL), and pancytopenia (Hb 6.3 mg/dL). Of note, he remained asymptomatic until 2 days prior to labs when noted to have periorbital and lower extremity edema associated with decreased urine output. Altogether biopsy revealed foot process effacement without definitive evidence of segmental sclerosis. Infectious workup including viral studies for SARS-CoV-2 were negative. He received methylprednisolone 1 g IV for 3 days, then 500 mg IV for 3 days, then 250 mg IV for 3 days and was discharged with prednisone 375 mg/2 weekly x2, and an oral prednisone taper. During week 4 of PP concurrent with prednisone taper, the patient appeared clinically well with noted improvement in labs: UPCR 0.55 mg/mg, Scr 0.57 mg/dL, and serum albumin 3.5 g/dL. He is currently undergoing wean of PP and steroids.

**Discussion:** While there are isolated reports of new onset or recurrence of proteinuric kidney disease after an mRNA COVID-19 vaccine, to our knowledge, this is the first report of FSGS recurrence in a kidney transplant recipient. Although causality is not proven, the temporal relationship strongly suggests an association between the vaccine and disease recurrence. Compared with prior reports, our patient presented somewhat later, ~1 month after dose #2 as compared to within 2 weeks after dose #1. Although the risk-benefit ratio of COVID vaccination for kidney transplant recipients remains favorable and vaccine is encouraged by national clinical guidelines, close monitoring after COVID vaccine for kidney transplant patients at risk for disease recurrence is warranted.

**Case Description:** 63-year-old Hispanic female with past medical history of hypertension, psoriatic arthritis presented to the hospital with gross hematuria for 6 weeks starting 3 days after 2nd dose of Pfizer COVID vaccine. Her PCP had sent her to ER 5 days after onset of hematuria as had noted a creatinine (Cr) of 1.6 with >3+ protein and >20 RBCs on urinalysis suspicious for nephrotic syndrome. On review she had serum Cr of 0.45 about 4 months ago with no proteinuria or hematuria before. In the ER she was given antibiotics for urinary tract infection and outpatient referral for nephrology. She could not make the outpatient appointment and with continued gross hematuria for a month, she presented to the ER again where she was noted to have Cr of 10 mg/dL and urine protein ratio of 7.5 mg/mg. Renal imaging including CT urogram was normal. Renal biopsy showed IgA nephropathy, M1S0E0T1C1 with a fibrocellular crescent and acute tubular injury. Steroid therapy was initiated. Hemodialysis was stopped 38 days after the start of therapy. At dialysis cessation, serum creatinine was 1.4 mg/dL with a marked decreasing in spot microalbuminuria.

**Discussion:** We suspect that this case of MCD might be related to the Oxford-AstraZeneca SARS-CoV-2 vaccine injection. To the best of our knowledge, this would be the first published case of MCD related to this vaccine. However, MCD has been described after mRNA vaccines, including 3 cases after the Pfizer/BioNTech SARS-CoV-2 vaccine. The fact that MCD is now described with different types of SARS-CoV-2 vaccines argues that MCD may be an immune-mediated disease, likely related to vaccination in general. Although minimal change disease (MCD) has been described following the Pfizer-BioNTech SARS-CoV-2 vaccine, no cases are described to our knowledge after the Oxford-AstraZeneca vaccine SARS-CoV-2 vaccine.

**Case Description:** A 71-year-old man known for dyslipidemia and a serum creatinine of 0.7 mg/dL presented with nephrotic syndrome and acute kidney injury 13 days after receiving the first injection of the Oxford-AstraZeneca SARS-CoV-2 vaccine. On admission, urine analysis revealed 2321 mg of protein per milliliter, ~1 month after dose #2 and significant hematuria as well as granular casts. His serum albumin and creatinine were 2.8 g/dL and 10.6 mg/dL, respectively. Polymers chain reaction for SARS-CoV-2 was negative. A workup to exclude auto-immune disease, active infection and neoplasia was negative. A kidney biopsy was performed 4 days after admission and 17 days after vaccination. It showed minimal change disease with acute tubular injury. Steroid therapy was initiated. Hemodialysis was stopped 38 days after the start of therapy. At dialysis cessation, serum creatinine was 1.4 mg/dL with a marked decreasing in spot microalbuminuria.

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the biopsy, we prescribed Lisinopril 5 mg daily for control of proteinuria. We did not prescribe high dose steroids since the mild nature of the case and lack of inflammatory infiltration. The patient continues to do well without symptoms. Her most recent labs show preserved renal function and spot proteinuria reduced to 1 g/d.

Discussion: The current case raises questions about the potential association of IgA Nephropathy (IgAN) flare-up due to COVID-19 infection. This may be due to increased IgA levels or activation of the complement system. A possible mechanism includes an aberrant mucosal immune response to the initial SARS-COV-2 infection that she contracted in December 2020. This could have then predisposed her to IgA nephropathy after the administration of the vaccine. The virus’ spike protein or other factors may trigger an aberrant mucosal immune IgA response which can then lead to the onset and progression of IgA nephropathy. Further case series are needed to establish a more definitive association of the COVID-19 vaccine with IgA nephropathy.

PO0111
IgA Nephropathy Flare Following COVID-19 Vaccination
Mohammad Hamzha, Kelly H. Beers. Albany Medical Center, Albany, NY.

Introduction: IgA nephropathy is the most common cause of primary glomerulonephritis in people of Asian origin. It is characterized by mesangial deposition of IgA which activates Lectin and Alternative pathways that cause glomerular damage which results in hematuria and proteinuria. Untreated disease can progress to chronic kidney disease, and even end-stage kidney disease.

Case Description: We describe a case of a 28-year-old male of Chinese descent who has a biopsy-proven diagnosis of IgA nephropathy (Oxford classification M1 E0 S1 T0 C1). Patient was maintained on Losartan 100 mg daily with proteinuria under 500mg per day.

Discussion: After COVID-19 Infection

After COVID-19 Infection

PO0113
A Biopsy-Confirmed Case of IgA Nephropathy Flare-Up with Gross Hematuria and AKI Following SARS-CoV-2 Vaccination Successfully Treated with Steroid Therapy
Shota Watanabe, Shuling Zheng, Arash Rashidi. University Hospitals, Cleveland, OH.

Introduction: The flare of immune-mediated disease (IMDs) following SARS-CoV-2 vaccination is a rare adverse event following immunization (AEFI). A few cases of suspected IgA nephropathy (IgAN) flare-up, causing gross hematuria without an increase in Cr, have been reported, and they all resolved without treatment. Here we report a biopsy-confirmed case of IgAN flare-up with AKI following mRNA-1273 vaccination, which was successfully treated with steroid therapy.

Case Description: A 54-year-old female with history of IgAN after strep throat infection that was diagnosed with renal biopsy in 2006. Other significant co-morbidity includes obesity (BMI 31.6), hypertension, and GERD. No prior documented infection with COVID-19. She was on enalapril 20mg daily, hydrochlorothiazide 12.5mg daily, and propranolol 120mg daily. Her baseline creatinine level was 1.2. Urinalysis was positive for 3+ protein, 3+ blood, and RBC 15 /HPF. The total urine protein to Cr ratio was 1.03.

Two days after receiving the second Moderna mRNA-1273 vaccine, she developed gross hematuria, which resolved in 2 days. Follow-up Cr increased to 3.04 one week after receiving the second dose of vaccine. The urinalysis showed 1+ protein, 3+ blood, RBC 50 /HPF. The total urine protein to Cr ratio was 0.67. The renal ultrasound was unremarkable. Repeat kidney biopsy showed IgAN mesangial deposition, focal segmental and focal global glomerulosclerosis, mild interstitial fibrosis and tubular atrophy, and mild arteriolar hyalinosis. The patient was started on prednisone 60mg daily. Shortly after she was started on prednisone, Cr level started getting better. In 3 weeks Cr level was down to 1.7.

Discussion: This is the first reported case of biopsy-proven IgAN flare-up after SARS-CoV-2 vaccination that caused AKI. Corticosteroid is an effective treatment, promptly improving Cr. IgAN exacerbation after SARS-CoV-2 vaccination should be closely monitored for frequency and consequence to further elucidate AEFI of the novel vaccine.

PO0114
New Diagnosis of Glomerulonephritis and Relapse of Prior Glomerulonephritis Post mRNA COVID-19 Vaccination
Nattawat Klinmit, Ziad Zoghby, Fernando C. Fervenza, Ladan Zand. Mayo Clinic Minnesota, Rochester, MN.

Introduction: Messenger RNA COVID-19 vaccine is more effective than traditional vaccines due to superior immune activation. However, the impact of mRNA COVID-19 vaccine on glomerulonephritis (GN) is limited. We report 4 cases of patients who developed new or had relapse of GN post vaccination.

Case Description: Case 1: A 43-year-old male with prior COVID-19 infection and baseline serum creatinine (SCr) of 1.2 mg/dl received Moderna vaccine 9 months after recovering from COVID-19 infection. Two weeks after the 1st dose, Scr increased to 1.5 mg/dl. He received 2nd dose 2 weeks later and Scr 3 days after was 2.7 mg/dl. Urinalysis (UA) showed 21-30 RBC/hpf and 24 hr urine protein (UP) was 14.4 g. A kidney biopsy revealed IgAN with moderate interstitial nephritis. He was treated with prednisone and ramosipril. Case 2: A 66-year-old male with atrial fibrillation with baseline SCr 1.1 mg/dl received 1st dose of Moderna vaccine and two weeks later Scr was 1.5 mg/dl. Eight weeks after the 2nd dose, Scr was 2.4 mg/dl. UA showed 51-100 RBC/hpf and 24 hr urine protein (UP) was 14.4 g. A kidney biopsy revealed IgAN with moderate interstitial nephritis. He was treated with prednisone and ramosipril. Case 2: A 66-year-old male with atrial fibrillation with baseline SCr 1.1 mg/dl received 1st dose of Moderna vaccine and two weeks later Scr was 1.5 mg/dl. Eight weeks after the 2nd dose, she developed leg edema with albumin 2.2 g/dl, 24 hr UP 10 g/dl, and Scr 0.6 mg/dl. A repeat kidney biopsy showed focal segmental glomerulosclerosis, tip variant. She was treated with prednisone and tacrolimus. Case 4: A 39-year-old male with PLAS-2 membranous nephropathy who was in remission and off immunosuppressive therapy for 1.5 years received 2 doses of Pfizer vaccine. Two weeks after the 2nd dose, he developed leg edema with albumin 2.2 g/dl, 24 hr UP 10 g/dl, and Scr 0.6 mg/dl. A repeat kidney biopsy showed focal segmental glomerulosclerosis, tip variant. He was treated with prednisone and tacrolimus. Case 4: A 39-year-old male with PLAS-2 membranous nephropathy who was in remission and off immunosuppressive therapy for 1.5 years received 2 doses of Pfizer vaccine. Two weeks after the 2nd dose, he developed leg edema with albumin 2.2 g/dl, 24 hr UP 10 g/dl, and Scr 0.6 mg/dl. A repeat kidney biopsy showed focal segmental glomerulosclerosis, tip variant. He was treated with prednisone and tacrolimus. Case 4: A 39-year-old male with PLAS-2 membranous nephropathy who was in remission and off immunosuppressive therapy for 1.5 years received 2 doses of Pfizer vaccine. Two weeks after the 2nd dose, he developed leg edema with albumin 2.2 g/dl, 24 hr UP 10 g/dl, and Scr 0.6 mg/dl. A repeat kidney biopsy showed focal segmental glomerulosclerosis, tip variant. He was treated with prednisone and tacrolimus.

Discussion: New cases and relapse of GN can present shortly after mRNA COVID-19 vaccination. Messenger RNA COVID-19 vaccine may be associated with reactivation of known glomerulonephritis or unmask presence of previously undiagnosed GN such as IgAN possibly due to potent immune activation. However, mechanism remains unknown and additional studies are needed.
PO0115
Impact of the COVID-19 Pandemic on Kidney Diseases Requiring Renal Biopsy: A Single-Center Observational Study
Bjoern Tampe, 1 Samy Hakroush, 1 Nephrology and Rheumatology, University Medical Center Göttingen, Göttingen, Germany; 2Institute of Pathology, University Medical Center Göttingen, Göttingen, Germany.

Background: The coronavirus disease-2019 (COVID-19) pandemic impacted healthcare services for kidney disease patients. Lockdown and social distancing were mandated worldwide. Consequently, closure of medical services. The diagnostic and confirmatory kidney diseases may have been delayed during the COVID-19 pandemic because non-urgent tests and visits were postponed due to closure of medical services during the lockdown.

Methods: We here report the impact of the COVID-19 pandemic on a total number of 209 native kidney disease patients requiring renal biopsy for diagnosis in a retrospective observational study from a tertiary hospital in Germany.

Results: The lockdown period in March and April 2020 primarily affected patients admitted to the normal medical ward with a compensatory increased rate of renal biopsies in May. In addition, there was a shift towards more patients admitted with proteinuria and hemoglobinuria during the COVID-19 pandemic. This phenomenon of an increased number of patients with hemoglobinuria during the COVID-19 pandemic was specifically observed in a subgroup with hypertensive nephropathy requiring renal biopsy, not attributed to the COVID-19 lockdown period itself.

Conclusions: To our knowledge, this is the first report of identifying a subpopulation susceptible to closure of medical services during the COVID-19 pandemic and diagnostic delay of specific kidney diseases. Therefore, the COVID-19 pandemic should be regarded as a risk factor especially in patients with diseases other than COVID-19 primarily admitted to the normal medical ward.

PO0116
Tip Lesion Variant of Focal and Segmental Glomerulosclerosis (FSGS): A Case Report in a Patient with COVID-19
Rita S. Afonso, Ana Cabrita, Ana P. Silva. Centro Hospitalar do Algarve EPE, Faro, Portugal.

Introduction: Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection. Published cases report acute tubular injury as the most common pathological finding in these patients. Glomerular disease has been reported in a minority of patients, with collapsing focal segmental glomerulosclerosis being the most common. Nonetheless, the exact underlying etiopathogenesis is sparse and inconclusive. The authors present a case of a patient diagnosed with a tip lesion variant of focal and segmental glomerulosclerosis (FSGS) and concomitant SARS-CoV-2 infection.

Case Description: A 43-year-old African woman, with no known past medical history, presented to the emergency department 5-6 days after the onset of fatigue, cough, hypoaesthesia, myalgia, dyspnea, nausea and vomiting. Laboratory tests confirmed SARS-CoV-2 infection. Despite fluid therapy, there was an elevation of serum creatinine from 1.1 to 1.6mg/dl and the urinalysis was positive for protein (4+) and blood (2+). The urinary sediment revealed 3 red blood cells per high-power field. The urinary protein/creatinine ratio was approximately 13 g, subsequently confirmed with a 24-hour urine collection (13445 mg/24hours). All immunological tests were negative with the exception of hepatitis B serology (positive for HBV past infection). Renal ultrasonography showed a right kidney of 105 mm and a left kidney measuring 99 mm with important reduction of corticomedullary differentiation. After cure criteria for COVID-19, the proteinuria was 1022 mg/24h. The kidney biopsy revealed a tip lesion variant of focal and segmental glomerulosclerosis (FSGS). Low dose angiotensin converting enzyme inhibitors were started but no corticotherapy due to spontaneous regression of proteinuria. The patient returned home 20 days later with normalisation. After 1 month, serum creatinine levels and 24-hour urine protein decreased to 1.1 mg/dl and 1060 mg, respectively.

Discussion: To our knowledge, this is the first case report of a patient with tip lesion variant of focal and segmental glomerulosclerosis (FSGS) possibly associated with COVID-19 disease. More data from kidney biopsies will further elucidate about pathologic processes associated with kidney injury and glomerular involvement in SARS-CoV-2 infection.

PO0117
Cause or Not: IgA-Dominant Infectious-Related Glomerulonephritis in a Patient Infected with COVID-19
Alexander Barrero-Arvelo, 1 Lisa M. Sebastian, 2 Roberto L. Collazo-Maldonado. 3Methodist Dallas Medical Center, Dallas, TX; 2Dallas Nephrology Associates, Dallas, TX.

Introduction: IgA dominant infectious related glomerulonephritis (IgAD-IRGN) is an uncommon variant of IRGN. It has been mostly associated with S.aureus infections. In the COVID-19 Era, there has been one case of IGAD-IRGN related to COVID. This is a case of IGAD-IRGN in a patient infected with COVID-19.

Case Description: 51 y/o male with no previous medical history who presented with a 3 day history of generalized swelling. Patient had no known medical problems and was not taking any medications. He reported drinking 3 beers daily. Denied any recent illness or sick contacts. At ED, the patient was found with anasarca and uncontrolled blood pressure. Initial blood tests showed normal renal function with hypoalbuminemia (2.9g/dL). UA showed active sediments and nephrotic range proteinuria of about 4 g/ d. Subsequent tests, including serology, were negative. Labs were subsequently normal, except for elevated ESR (105), low C4 (12), normal C3 (95) and elevated RF (44). ANA, HIV, HCV, light chain ratio, cryoglobulins and ANCA were negative. UIPEP showed faint IgG kappa, showed hazy intimal opaciities with a perihilar distribution. Pre-biopsy COVID molecular testing came back positive. He was diuresed aggressively and received losartan for BP control. A kidney biopsy was performed and revealed margin MPG pattern with IF strongly positive for IgA in addition to weaker staining for C3, and IgG. EM showed subepithelial humps with few mesangial and subepithelial deposits. The diagnosis of IgA-Dominant immune complex mediated glomerulonephritis consistent with IRGN was made.

Discussion: IGAD-IRGN is a rare variant of IRGN that has been mostly associated with S.aureus infections. In this case, the recent COVID infection in this patient could reasonably explain the finding of IGAD-IRGN on kidney biopsy. IGAD-INF related GN has been reported only once in the literature. Up until recently, most cases of COVID related kidney injury have been associated to ATN and collapsing FSGS. A recent reactive IgA nephritis, test for COVID in kidney tissue was sent, which is pending. The time of this submission. If confirmed positive, this could be the second confirmed case COVID related IGAD-IRGN. It is important for nephrologists to include IGAD-IRGN in the differential diagnosis in a COVID patient with nephrotic syndrome. Renal Biopsy is of utmost importance for diagnosis.

PO0119
De Novo Henoch Schönlein Purpura (HSP) Post Kidney-Pancreas Transplant Triggered by COVID-19 Infection
Minyee He, Iris J. Lee, Ilay Rahman, Serban Constantinescu. Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: Histologic recurrence of immunoglobulin A (IgA) nephropathy after kidney transplant is common, whereas development of HSP is rare post-kidney transplant. We describe a case of HSP with cutaneous and renal allograft findings, triggered by COVID-19 (SARS-CoV-2) infection.

Case Description: A 53-year-old African American (AA) male with history of ESRD secondary to diabetic nephropathy, underwent simultaneous pancreas-kidney transplantation three months later. He maintained good graft function post-transplant with one episode of hyperkalemia requiring dialysis. Four months post-transplant, he developed lower extremity pain, hand and wrist pain, acute kidney injury and new onset nephrotic syndrome with 6.6g proteinuria and microscopic ischemic hematuria. He had detectable SARS-CoV2 RNA in the nasopharyngeal speculum and mild multifocal pneumonia treated with levodopa and Remdesivir. Serologic work-up for nephrotic syndrome was negative. A skin biopsy demonstrated leukocytoclastic vasculitis. Renal allograft biopsy showed membrane proliferative and sclerosing glomerulonephritis with dominant IgA staining by immunofluorescence, consistent with IgA nephropathy. He received pulse dose steroids for 3 days and improvement in kidney, skin function and reduction of his proteinuria to 0.6 g 4 months after steroid treatment.

Discussion: We postulated that our patient developed de novo HSP and nephrotic syndrome as a result of COVID-19 infection. Podocytopathy and nephrotic syndrome linked to viral infection have been well described, particularly in AA patients with high-risk APOL1 genotype. Key cytokines known to be elevated in COVID19 infection can drive autoimmune responses, such as interferon and IL-6. Cytokine release, uncontrolled activation of both innate and adaptive immune cells, along with genetic variants likely pre-dispose patients to the development of glomerular disease mediated by various immune mechanisms. Published biopsy series consistently demonstrate acute tubular injury as the most common renal manifestation of COVID-19 manifestation, however, new onset autoimmune diseases such as IgAN may also be triggered by COVID infection. HSP can be a rare complication of COVID-19 by occurring post-COVID disease and systemic autoimmunity should be recognized as a complication of COVID-19, regardless of the presence or absence of pulmonary findings.

PO0119
COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Case Series of 10 Cases from Dominican Republic
Denazr Atizol Rodriguez, 1 Nathali E. Bencosme, 1 Anthony J. Gutierrez, 1,2 Annette G. Garcia Delgado, 2 Eliana Dina Batlle. 3, 4 Pontificia Universidad Católica Madre y Maestra Facultad de Ciencias de la Salud, Santiago De Los Caballeros, Dominican Republic; 5Hospital Metropolitano de Santiago, Santiago de los caballeros, Dominican Republic.

Introduction: The coronavirus disease 2019 (COVID-19) has caused tremendous impact mainly due to the significant morbidity and mortality caused by the virus. It is currently known that the probability of becoming seriously ill from this disease is higher in older adults, in people with pre-existing comorbidities, and those with a suppressed immune state. Therefore, transplant patients are not the exception. Considering the importance of this topic and the scarce information on the outcome of this type of patient, especially in Latin America, this series of cases is focused on our experience with 10 kidney transplant patients hospitalized for COVID-19.

Case Description: The age range of the patients was 41 to 68 years, where 8 of these were men. The most common admission symptoms were fever (20%), myalgia/arthritis (50%), and headache (50%). The most prevalent laboratory findings were lymphocytopenia and increased inflammatory markers such as D-dimer, LDH, procalcitonin, erythrocyte sedimentation, and ferritin. General management included supportive treatment, statins, and antithrombotic therapy, while the specific treatment options were hydroxychloroquine, antivirals, corticosteroids, intravenous ig, tocifasitib, and convalescent plasma. All the patients improved and were discharged. Two of them went to the ICU and only one required mechanical ventilation. The majority of the patients had ESRD secondary to diabetic nephropathy. 5 patients remained with their baseline immunosuppression without dose reduction or suspension.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: kidney transplant recipients are more susceptible to infections, along with increasing disease severity. At the same time their immunosuppressed state might lead to the inflammatory response following this type of infection. Decisions were based on stopping or attenuating the viral load and the systemic inflammation caused by this virus, but at the same time protecting against acute allograft rejection and the coagulation with other pathogens. Our findings suggest that the use of statins and antimicrobial prophylaxis in all hospitalized transplant patients may be beneficial to reduce the risk of mortality in patients with COVID-19 infection. Also, the maintenance of immunosuppressive therapy was not associated with worse outcomes.

PO0120
ANCA Vasculitis Presenting as Hemothrosis Post COVID-19 Infection
Surya Manivannan, Koyal Jain. University of North Carolina System, Chapel Hill, NC.

Introduction: COVID-19 infection has been suggested to be a trigger for a de-novo autoimmune response. This case represents one of a few reported cases of ANCA vasculitis developing after a COVID infection.

Case Description: A 41-year-old female with a history of chronic sinusitis (not vasculitis related), obesity, right pulmonary sequestration, and mild COVID-19 infection 1-month prior manifesting as only mild cough with loss of taste and smell, was admitted with a 2-week history of progressive cough productive of blood-tinged sputum and lower extremity neuropathy. CTA of her chest showed air space opacities in right lower lobe concerning for bacterial superinfection in a host with altered pulmonary architecture. She was treated for presumed community acquired pneumonia. A week later, she presented with worsening hemothrosis and respiratory failure requiring intubation, which escalated quickly to needing extracorporeal membrane oxygenation (ECMO). Extensive bilateral airspace infiltrates due to diffuse alveolar hemorrhage and a PR3-ANCA level of 175 U/ml were strongly suggestive of a new diagnosis of ANCA-vasculitis (granulomatosis with polyangiitis). Her renal function remained normal, and urine sediment had no findings to indicate an ongoing concurrent nephritic process. She was given high dose pulse intravenous steroids, recombinant factor VII, 7 sessions of daily plasma exchange, intravenous tranexamic acid, and 1 dose of Cytoco 500 mg/m2. She briefly had clinical improvement and required decreased ECMO support, but unfortunately, she later developed worsening pulmonary hemorrhage and hypotension, which was attributed to acute respiratory distress syndrome and thrombocytopenia, as opposed to immune mediated capillaritis. After 2 weeks of treatment, she was terminally decannulated.

Discussion: This is a rare case of ANCA-vasculitis likely triggered by COVID-19 infection. The presence of peripheral neuropathy indicates that she probably had extrapulmonary manifestations of vasculitis, although she had no evidence of renal involvement. This case report demonstrates that a high index of suspicion is needed for a new diagnosis of ANCA-vasculitis in patients with a prior history of COVID-19 infection to allow for prompt diagnosis and appropriate management.

PO0121
Deep Learning for Subphenotype Identification in COVID-19-Associated AKI
Suraj Akhil, Akhil Paranjpe, Karandeep Singh, Lili Chan, Steven G. Coca, Girish N. Nadkarni. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Acute kidney injury (AKI) is common in COVID-19 and associated with increased adverse outcomes. COVID-associated AKI (COVID-AKI) pathophysiology is heterogeneous, and deep learning may discover subphenotypes.

Methods: We used data from 5 New York City hospitals from adults admitted between March 20-March 21 with COVID and AKI, excluding patients with kidney failure. An autoencoder compressed 58 features containing comorbidities, the first laboratory values and vital signs within 48 hours of admission for unsupervised K-means clustering.

Results: There were 1634 patients with COVID-AKI and discovered 3 subphenotypes. Subphenotype one had 576 patients (35%); two had 635 patients (39%); and three had 423 patients (26%) (Table 1). Subphenotype three had the lowest median values and vital signs within 48 hours of admission for unsupervised K-means clustering. Heterogenous, and deep learning may discover subphenotypes.

Conclusions: There are distinct subphenotypes in COVID-AKI indicating the heterogeneity of this condition.

Funding: NIDDK Support

Table 1. Demographics of COVID-Associated AKI Subphenotypes.
COVID-19: Health Systems and More

**PO0125**

**AKI Secondary to Atypical Hemolytic Uremic Syndrome Caused by COVID-19**

Rahul R. Abraham, Hugo Akabane. LSU Health Shreveport, Shreveport, LA.

**Introduction:** Atypical Hemolytic Uremic Syndrome (aHUS) can be triggered by viral infections. So far there has been little data on COVID-19 infection-causing aHUS. We present one such case of acute kidney injury (AKI) secondary to aHUS with COVID-19 infection and its outcome.

**Case Description:** A 55-year-old woman presented with altered mental status and shortness of breath from 2-3 days. The patient tested positive for the COVID-19 virus. Labs showed creatinine of 4.8 mg/dL from a baseline of 0.8 mg/dL, with a hemoglobin of 8.9 g/dL and a platelet count of 20,000/µL. Peripheral smear showed evidence of large number of schistocytes and thrombocytopenia. Haptoglobin and reticulocyte counts were 2.8 g/dL and 0.1 respectively. In view of the above findings, there was high suspicion for Thrombotic thrombocytopenic purpura (TTP). Her PLASMIC score was 6. Treatment with plasma exchange therapy (PEX) and steroids was initiated but there was no significant clinical improvement. An ADAMST13 level of 0% was obtained, and resulted in positive finding for TTP. Due to lack of evidence of TTP eculizumab was started for suspected aHUS. She responded remarkably well (within days) with mentation returning to baseline, hemoglobin stabilizing, platelet slowly trending towards normal and peripheral smear, labs showing no signs of hemolysis, and an improvement in her RFP. At 5 month follow-up, the patient eventually progressed to end-stage renal disease had to be placed on regular dialysis.

**Discussion:** aHUS is a rare variety of thrombotic microangiopathy (TMA) which results in a classic triad of Coombs negative hemolytic anemia, renal injury, and thrombocytopenia. aHUS has a mortality rate of 25%. 50% of patients eventually progress to ESRD or have irreversible brain damage. Multiple triggers have been identified including various non-enteric infections, viruses, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions. At the time of writing this case report, there is only one other case report of COVID-19 virus-induced aHUS resulting in AKI. In AKI renal damage is thought to be caused by microthrombi formation in the kidney vasculature. Endothelial damage is further escalated by anaphylatoxins produced by complement activation. aHUS induced AKI is an alternate mechanism for COVID-19 to cause AKI requiring eculizumab for optimal treatment.

**PO0126**

**Cryoglobulinemia in the Setting of COVID-19 AKI**

Emily L. Ward, Gunjan Garg. University of Louisville, Louisville, KY.

**Introduction:** COVID-19 is due to SARS-CoV-2 a single stranded RNA virus with respiratory and epithelial cell targets. As COVID19 has reached pandemic proportions, complicating AKI is common. Pathogenesis is varied and multifactorial but acute tubular injury is most common. Glomerular pathology is possible but not well defined.

**Case Description:** 66YOM with HTN, Stage III CKD, & COVID19 hypoxemic respiratory failure complicated by AKI & nephritic syndrome. Cr peaked at 5mg/dL. He required CRRT for volume overload & acidosis. Labs showed low C3 & type I cryoglobulinemia. IgG deposits indicative of cryoglobulins on EM. He received pulsed solumedrol then 5 sessions of PLEX. Renal recovery with good urine output, dialysis discontinued. Cr down to 2.2mg/dL post PLEX.

**Discussion:** Cryoglobulinemia is due to cold immunoglobulin precipitation. Type I is associated with malignancy or hematologic disease and Types II & III have aHUS, immune complex disease, etc. Our patient had Type I IgG cryoglobulinemia without evidence of malignancy. BM bx had 10% abnormal plasma cells, perhaps due to plasma cell dyscrasia of cryoglobulinemia. A prior case series reported COVID19 incident MGUS. Patients had monoclonal IgG or IgGk but no mentioned renal injury. They hypothesized gammopathy driven cryoglobulinaemia, our patient’s renal manifestations fit aHUS. Our case illustrates the benefit of biopsy to identify additional treatment options and the reality that timely biopsy isn’t always be safely obtained. In COVID19 patients respiratory or hematologic status can make biopsy unsafe which may limit defining associated glomerular pathology.
PO0127
Antibody and T Cell Reactivity Response After SARS-CoV-2 BNT162b2 mRNA Vaccine in Hemodialysis Patients: A Single-Center Experience from Sweden
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Background: The immune system is affected by uremia. Patients with end-stage kidney disease (ESKD) on hemodialysis treatment (HD) are vulnerable to infections, may have suboptimal response to vaccination and are at increased risk of contagious infections due to many health care contacts. They also have a high mortality from Covid-19 infection.

Methods: In 50 patients (mean age 69.4 years, 62% men) with ESKD and HD at Uppsala Academic Hospital, Sweden, administration of vaccine began in late Dec 2020 and the immune response was followed up four months later, in April/May 2021. IgG antibody test against Covid-19 (SARS-CoV-2) was performed against the nucleocapsid antigen (anti-N), positive only after illness, and against Spike antigen (anti-S) positive both after illness and after vaccination (quantitative method in routine diagnostics at the department of microbiology, Uppsala). T-cell reactivity testing against the Spike protein using ELISPOT technology measuring interferon-gamma activity was performed at ABC-labs, Solna.

Results: Out of 50 patients IgG antibodies to anti-S were detected in 37 (74%), 5 (10%) had a limit response and 8 (16%) were negative after two doses of vaccine. T-cell responses were detected in 29 (58%) and in 21 (42%) no response was detected. Of the 37 patients with antibody responses to anti-S, 25 (68%) also had a measurable T-cell response, 2 (40%) of 5 with limit value for antibody response and 2 (25%) of 8 had no antibody response. 27 (54%) had both an antibody and T-cell reactivity response. IgG antibodies to anti-N indicating a previous Covid-19 disease after 2 doses of vaccine were detected in 7 (14%) patients. 3 patients (6%) had tested PCR-Covid-19 positive before vaccination, 2 (40%) became positive during doses one and two. 4 (8%) had positive tests after two injections and all of them developed a mild disease. All 4 MCD patients were successfully treated with oral glucocorticoids, while the other podocytopathies to vaccine-induced complications. Temporal association is essential for diagnosis; prompt accurate diagnosis benefits treatment and response.

Conclusions: A majority of patients with ESKD and HD develop a B- and/or T-cell response after vaccination to identify patients are not protected and where to need to take other measures to protect them from infection. In these patients, a third vaccine dose with another type of vaccine could be justifiable.

Funding: Clinical Revenue Support

PO0128
COVID-19 mRNA Vaccine-Associated Autoimmunity Presenting as Minimal Change Disease and Membranous Nephropathy
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Background: Vaccine-triggered complications, including autoimmune diseases and minimal change disease (MCD), were reported during recent COVID-19 vaccine rollout. Anti-nephrin autoantibodies were described in nephrotic syndrome (NS) with kidney biopsy (Kbx)-proven MCD. Therefore, we examined patients with COVID-19 vaccine-associated NS for anti-nephrin autoantibodies.

Methods: 5 patients presenting with nephrotic-range proteinuria 1-3 weeks after COVID-19 vaccine and a Kbx were identified (3 Pfizer/BioNTech, 2 Moderna). Past medical history and lab tests including serum creatinine (sCr), urine protein-to-creatinine ratio (UPCR), and serological workup were recorded. Kbx were routinely evaluated by light microscopy (LM), immunofluorescence microscopy (IF), and electron microscopy (EM), followed by confocal examination of relative IgG and nephrin localization in all patients; serological studies for anti-nephrin antibodies using human glomerular extract and recombinant nephrin extracellular domain were performed using plasma available on 2 patients.

Results: In all patients, sCr was 0.5-1.2 mg/dL and UPCR 4.5-7.6 g/g. 1 patient had MCD in remission diagnosed 6 months prior; others had no relevant PMH. All workup was negative, except low positive ANA in 2 patients. On Kbx, diagnosis of MCD was made in 4 and stage 1 membranous nephropathy (MN) in 1 patient(s) (serum albumin 2.0-2.3 g/dL in MCD and 3.5 g/dL in MN patient(s)); all had mild chronic changes. All 4 MCD patients had fine granular punctate podocyte staining for polyclonal IgG colocalizing with nephrin by IF and diffuse FPE by EM; in 1 patient plasma was saved during NS and was serologically positive for anti-nephrin. The MN patient had 3+ fine granular IF staining for polyclonal IgG and PLAC2 along GBMs with sparse superficial subepithelial electrondense deposits on EM, and was serologically positive for anti-nephrin. All MCD patients were successfully treated with oral glucocorticoids, while the MN patient was monitored closely under RAAS blockade.

Conclusions: COVID-19 mRNA vaccines can trigger de-novo or relapsing anti-nephrin- and PLAC2-mediated NS, thus adding both autoimmune-mediated podocytolysis to vaccine-induced complications. Temporal association is essential for diagnosis; prompt accurate diagnosis benefits treatment and response.

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PO0129
Real-World Effectiveness and Immunogenicity of BNT162b2 in Dialysis Patients
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Background: BNT162b2 (Pfizer/BioTech) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that BNT162b2 reduced risk of COVID-19 by 95%, however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with BNT162b2.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began a BNT162b2 vaccination series (January-March 2021) were matched (with replacement) to up to 4 previously unvaccinated controls based on age, diabetes status, sex, race, body mass index, date of first vaccine, US state of residence, and prior known COVID-19 diagnosis. Vaccine effectiveness was estimated by calculating the hazard ratio (HR) for time to polymerase chain reaction confirmed infection between vaccinated and unvaccinated patients over 3 follow-up intervals: days 1-21, 22-43, and 43+ after first dose of vaccine. Immunogenicity was measured in a subset of consented patients who completed the 2-dose BNT162b2 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of BNT162b2, and indirect chemiluminescence immunassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of >1 arbitrary unit (AU) were considered IgG+.

Results: We identified 12,169 patients who received BNT162b2 and were matched to 46,377 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.84 (0.68, 1.03), 0.63 (0.40, 0.93), and 0.21 (0.13, 0.35) during 1-21, 22-42, and 43+ days postvaccination, respectively. Among the 344 patients with postvaccination antibody measurements, 98.0% (95% CI: 95.2%-99.2%) were IgG+ (median: 63.3 AU of IgG).

Conclusions: Our results indicate that BNT162b2 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 were detected in nearly all patients vaccinated with BNT162b2 in whom antibodies were measured.

PO0130
Early Humoral Responses of Hemodialysis Patients After COVID-19 Vaccination with BNT162b2

Background: Patients receiving hemodialysis are at high risk for both SARS-CoV-2 infection and severe COVID-19. A life-saving vaccine is available, but sensitivity to vaccines is lower in dialysis patients. Little is yet known about antibody response after COVID-19 vaccination in this vulnerable group.

Methods: In this prospective study, we included 22 dialysis patients and 46 healthy controls from Heidelberg University. We measured anti-S1 IgG with a threshold index for detection >1, neutralizing antibodies, and antibodies against different SARS-CoV-2 fragments 17-22 days after the first and 18-22 days after the second dose of BNT162b2.

Results: After the first vaccine dose, 4/22 (18%) dialysis patients compared with 43/46 (93%) healthy controls developed positive anti-S1 IgG, with a median (IQR) anti-S1 IgG index of 0.2 (0.1-0.7) compared with 9 (4-16), respectively. SARS-CoV-2 neutralizing antibodies exceeded the threshold for neutralization in 42/48 (87%) dialysis patients compared with 43/46 (93%) in healthy controls, with a median (IQR) percent
inhibition of 11 (3–24) compared with 65 (49–75), respectively. After the second dose, 14/17 (82%) of dialysis patients developed neutralizing antibodies exceeding the threshold for viral neutralization and antibodies against the receptor-binding S1-domain of the spike protein, compared to 46/46 (100%) of healthy controls, respectively. The median (IQR) percent inhibition was 51 (32–86) compared to 98 (97–98) in healthy controls.

Conclusions: Patients receiving long-term hemodialysis show a reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2. The majority (82%) develop neutralizing antibodies after the second dose, but at lower levels than healthy controls.

Figure 1

PO0131

Humoral Response to the BNT162b2 Vaccine in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have high mortality from COVID-19 and immunity following vaccination remains uncertain. This study evaluated SARS-CoV-2 antibody response in HD patients following BNT162b2 COVID-19 vaccination compared to healthy care workers (HCW) and convalescent serum.

Methods: This single centre observational cohort study enrolled 142 HD patients and 35 HCW receiving the BNT162b2 vaccine. SARS-CoV-2 IgG antibodies to the spike protein (anti-spike), receptor binding domain (anti-RBD), and nucleocapsid protein (anti-NP) were measured in 66 HD patients receiving one vaccine dose, 76 HD patients receiving two vaccine doses, and 35 HCW receiving two vaccine doses.

Results: In HD patients receiving a single BNT162b2 dose, seroconversion occurred in 53/66 (80%) for anti-spike and 63/72 (88%) for anti-RBD by 28 days post dose, but only 15/66 (23%) and 4/66 (6%), respectively attained a robust response defined as reaching the median level of anti-spike and anti-RBD in convalescent serum. In patients receiving two doses of BNT162b2 vaccine, seroconversion occurred in 68/72 (96%) for anti-spike and 63/72 (88%) for anti-RBD by 2 weeks following the second dose while 52/72 (72%) and 43/72 (60%) reached median convalescent serum levels of anti-spike and anti-RBD. In HCW, 35/55 (100%) exceeded median levels of anti-spike and anti-RBD in convalescent serum 2–4 weeks post second dose.

Conclusions: This study found poor immunogenicity 28 days following a single dose of BNT162b2 vaccine in HD patients, supporting adherence to recommended vaccination schedules, and avoiding delay of the second dose in this population.

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PO0132

Comparative Effectiveness of Ad26.COV2.S vs. BNT162b2 for the Prevention of SARS-CoV-2 Infection Among Dialysis Patients

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Background: Elsewhere, we have demonstrated that the BNT162b2 vaccine (Pfizer/BioNTech) is highly effective in reducing risk of COVID-19 among real-world dialysis patients. Because individual vaccines may be differentially available (and acceptable) to patients, it is important to understand the comparative effectiveness of other agents, such as Ad26.COV2.S (Janssen).

Methods: This was a retrospective real-world comparative effectiveness study comparing two vaccination strategies ("use Ad26.COV2.S" versus "use BNT162b") among adult patients dialyzing at a large dialysis organization. Patients receiving Ad26.COV2.S were matched 1:1 to those initiating a BNT162b2 series based on age, race, US state of residence, calendar week of first vaccine receipt, and prior history of COVID-19. Follow-up time began the day after the first vaccine dose. The outcome of interest was the comparative rate of polymerase chain reaction-confirmed SARS-CoV-2 infections considered over 3 follow-up intervals: days 1-21, 22-42, and 43 post vaccination.

Results: There were 2683 matched pairs of patients who received a first dose of each vaccine. During days 1-21, the incidence rate was 1.26 infections per 1000 patient-weeks (pt-wks) among BNT162b2 recipients and 1.26 among Ad26.COV2.S recipients (incident rate difference [IRD]: 0.00; 95% confidence interval [CI]: -1.10, 1.10). During days 22-42, the incidence rate was 0.93 infections per 1000 pt-wks among BNT162b2 recipients and 0.40 among Ad26.COV2.S recipients (IRD: -0.53; 95% CI: -1.40, 0.30). After day 43, the incidence rate was 0.50 infections per 1000 pt-wks among BNT162b2 recipients and 0.50 among Ad26.COV2.S recipients (IRD: 0.00; 95% CI: -0.8, 0.8). Results were nearly identical when considering only patients without a prior history of COVID-19.

Conclusions: In a large contemporary cohort of dialysis patients, a "use Ad26.COV2.S" strategy versus a "use BNT162b2" strategy would be expected to yield no difference in additional cases of SARS-CoV-2 infections. Given similar effectiveness, vaccine allocation should be based on availability and logistical considerations.
PO0133
Predictors of Response to SARS-CoV-2 Vaccines Among Maintenance Dialysis Patients
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Background: Vaccines against SARS-CoV-2 are highly effective in the general population; however, their efficacy may be diminished in maintenance dialysis patients, a population particularly vulnerable to COVID-19. We assessed vaccine response in a national sample of maintenance dialysis patients.

Methods: Using retrospective clinical data, we assessed seroresponse to vaccine among maintenance dialysis patients cared for at 130 Dialysis Clinic, Inc (DCI) facilities. Via a clinical protocol available to early vaccinating facilities, antibodies against SARS-CoV-2 spike antigen were semi-quantitatively assessed beginning with the monthly blood draw at least two weeks after completion of a SARS-CoV-2 vaccine series. Vaccine response was defined as a titer ≥ 2 U/L, and logistic regression analysis was used to identify characteristics associated with response. Patients with history of COVID-19 prior to antibody assessment were excluded.

Results: Among 1,352 patients, 996 (74%) had a serologic response. Serologic response differed significantly by vaccine type: 314/386 (81%) among BNT162b2/Pfizer recipients, 615/665 (94%) among mRNA-1273/Moderna recipients, and 67/311 (22%) among Ad26.COV2.S/Janssen recipients. Age greater than 75, lack of hepatitis B immunity, immune-modulating medication, lower serum albumin, and COPD were associated with vaccine non-response (Figure). Conclusions: Serologic response to mRNA vaccines is robust among chronic dialysis patients, and the use of mRNA vaccines should be promoted aggressively in this vulnerable population. High rates of non-response to the Janssen vaccine warrant further study. Future research should evaluate the potential role for boosters and whether seroresponse corresponds with protection from COVID-19.

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PO0135
Anti-Spike Antibody Responses in Hemodialyzed Patients Vaccinated with Anti-COVID-19 BNT162b2 mRNA Vaccine
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Background: Patients under hemodialysis are at higher risk of developing severe complications upon SARS-CoV-2 infection and were prioritized in the Portuguese vaccination campaign.

Objectives: We performed a longitudinal analysis of antibody responses upon vaccination with BNT162b2 mRNA (Pfizer/BioNTech, Comirnaty) in a cohort of 156 hemodialyzed patients. Direct ELISA was used to quantify IgG, IgM and IgA anti-full-length Spike antibody levels against calibrated sera from naturally infected patients at three points: day of the first vaccine dose (t0); 3 weeks later (day of the second dose, t1), and 3 weeks after the second inoculation (t2) for 143/156 patients. Anti-n was also measured in t0 and patients anti-n positive were excluded.

Results: We observed that 90.9% of the patients developed anti-spike IgG antibodies after the second vaccine dose (t2). Seroconversion was remarkably low at t1 after the first vaccine dose with only 29.4% of patients developing anti-spike IgG antibodies. In addition to positivity, the second vaccine dose markedly increased IgG antibody levels. IgA levels were also higher at t2 with 83.9% of the patients achieving positivity while IgM positivity only reached 29.4%. Age showed a significant negative effect on the humoral response at t2 for anti-Spike IgG and for IgM, particularly over 60 years. Further analysis revealed that nine patients under immunosuppression therapies showed significantly lower humoral response along the vaccine schedule (p=0.005 at t1; p=0.008 at t2). Interestingly, the inability to develop anti-HBs antibodies upon hepatitis B vaccination frequently found in hemodialyzed patients was not correlated with lack of responsiveness to SARS-CoV-2 vaccination.

Conclusions: The large majority hemodialyzed patients showed a significant humoral response to BNT162b2 mRNA vaccination, but a sizable proportion of patients showed low antibody levels when compared to responses in the general population (medRxiv 2021.03.19.21253680).

PO0134
Humoral Responses to Single-Dose BNT162b2 mRNA Vaccination in Dialysis Patients Previously Infected with SARS-CoV-2

Background: Seroconversion rates following infection and vaccination are lower in dialysis patients compared to healthy controls. There is an urgent need for the characterization of humoral responses and success of a single-dose SARS-CoV-2 vaccination in previously infected dialysis patients.

Methods: We performed a dual-center study with 43 dialysis patients after BNT162b2 vaccination and 25 dialysis patients after PCR-confirmed COVID-19. Single-dose vaccination was performed in 13 previously infected patients. Anti-S1 IgG, neutralizing antibodies, and antibodies against various SARS-CoV-2 epitopes were measured 6 weeks after the first vaccination or onset of COVID-19 and 3 weeks after single-dose vaccination.

Results: Previously infected patients without vaccination showed a significantly higher neutralizing capacity than patients vaccinated twice (median [IQR] percent inhibition 88.0 (71.5–95.5) vs. 50.7 (26.4–81.0); P=0.018). After one single vaccine dose, infected individuals generated 15- to 34-fold higher levels of anti-S1 IgG than age- and dialysis vintage matched patients after infection or two-time vaccination with a median (IQR) index of 274 (151–791) compared to 18 (6–41) and 8 (1–21) (for both P<0.001). With a median (IQR) percent inhibition of 97.6 (97.2–98.9), the neutralizing capacity of SARS-CoV-2 antibodies was significantly higher in previously infected patients compared to other groups (for both P<0.001). Bean-based analysis showed high antibody reactivity against various SARS-CoV-2 spike protein epitopes after single-dose vaccination in previously infected patients.

Conclusions: Single-dose vaccination in previously infected dialysis patients induced a strong and broad antibody reactivity against various SARS-CoV-2 spike protein epitopes with high neutralizing capacity.
How Well Do Hemodialysis Patients Respond to the BNT162b2 mRNA COVID-19 Vaccine?

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Background: Hemodialysis patients as well as healthcare workers are considered to be in a high-risk category for SARS-CoV-2 infection and a priority for vaccination.

Methods: In a single-center outpatient hemodialysis unit, 46 healthcare workers and 216 patients were vaccinated simultaneously with BNT162b2 (BioNTech-Pfizer) vaccine. They received two doses, 21 days apart. The primary objectives were to evaluate the safety and efficacy of the vaccine.

Results: There were no major adverse events in either group. Lymphadenopathy was reported by some health workers. All (100%) individuals in the healthcare workers group developed a positive antibody response (anti-S IgG) after the second dose compared with 91.7% of patients. Among patients there was a significant negative correlation between anti-S levels and age after both, the first dose (R= -0.176; p<0.01) and the second dose (R= -0.193, p<0.005). There was also a significant negative correlation between anti-S and Charlson Comorbidity Index adjusted for age after both, the first dose (R= -0.150, p=0.028) and the second dose (R= -0.163, p=0.018). Finally, a negative correlation between anti-S and Body Mass Index was found after the first dose (R= -0.140, p=0.04).

Conclusions: Following vaccination, patients had a significantly lower anti-S response than healthcare workers. Age, Charlson Comorbidity Index and Body Mass Index negatively impacted the humoral response. However, with more than 91% response we believe that vaccination can be recommended strongly in the hemodialysis population.

Real-World Effectiveness and Immunogenicity of mRNA-1273 in Dialysis Patients

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Background: mRNA-1273 (Moderna) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that mRNA-1273 reduced risk of COVID-19 by 94.5%; however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with mRNA-1273.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began an mRNA-1273 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of mRNA-1273, and indirect chemiluminescence immunoassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of >1 arbitrary unit (AU) were considered IgG+.

Results: We identified 23,037 patients who received mRNA-1273 and were matched to 64,243 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.96 (0.79, 1.16), 0.51 (0.34, 0.75), and 0.27 (0.17, 0.42) during 1-21, 22-42, and ≥43 days postvaccination, respectively. Among the 329 patients with postvaccination antibody measurements, 96.0% (95% CI: 93.3%-97.9%) were IgG+ (median: 100.5 AU of IgG).

Conclusions: Our results indicate that mRNA-1273 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 were detected in nearly all patients vaccinated with mRNA-1273 in whom antibodies were measured.
PO0140

Time-Dependent Evolution of IgG Antibody Levels After First and Second Dose of mRNA-based SARS-CoV-2 Vaccination in Hemodialysis Patients: A Multicenter Study

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Background: Vaccination programs are essential for the containment of the COVID-19 pandemic, which has affected significantly the hemodialysis population. Early reports suggest a reduced immunologic response to COVID-19 vaccines in dialysis patients, in spite of a high degree of seroconversion. We aimed to identify risk factors for a reduced efficacy of an mRNA vaccine in a cohort of hemodialysis patients.

Methods: In a multicenter study, including 294 Portuguese hemodialysis patients from multiple centers who had received 2 doses of BNT162b2 with a three week interval, IgG-class antibodies against SARS-CoV-2 spike protein were determined 3 weeks after the first dose (M1) and 6 weeks after the second dose (M2). The threshold for seroconversion was 10 U/mL. Demographic and clinical data was retrieved from a quality registry. Adverse events were registered using a questionnaire.

Results: At M2, seroconversion was 93.3%, with a median antibody level of 197.5 U/mL (IQR: 122.3–327.0) and a median increase of 180.0 U/mL (IQR: 82.9–2244.6) from M1. Age (beta -8.9, 95% CI: -12.8 to -4.9; p = 0.0001), ferritin >600 ng/mL (beta 183.93; 95% CI: 30.7 to 500.88; p = 0.03) were independent predictors of SARS-CoV-2 antibody levels after two vaccine doses. Plasma albumin >3.5 g/dL independently predicted the increase of antibody levels between both doses (OR 14.72; 95% CI: 1.38 to 157.45; p = 0.03). Only mild adverse reactions were observed in 10.9% of patients.

Conclusions: The COVID-19 vaccine BNT162b2 is safe and effective in hemodialysis patients. Besides age, iron status and nutrition are possible modifiable modulators of the immunologic response to COVID-19 mRNA vaccines.

PO0141

Antibody Response to COVID-19 Vaccine in Peritoneal Dialysis (PD) Patients: A Single-Center Study

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Background: In initial published reports of dialysis patients, response to COVID-19 vaccination tends to be lower as compared to general population. To date, these studies were primarily focused on hemodialysis (HD) patients. We studied the factors associated with COVID-19 vaccine humoral response in PD patients.

Methods: Our research setting was a single-center academic institution in New York City. We included patients on PD who received the COVID-19 vaccine. Response was assessed at a median of 4 weeks after completing the full vaccination series by chemiluminescent sandwich immunoassay. Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used to compare characteristics with COVID-19 vaccine response across PD patients. An interim analysis of a quality improvement project characterizing the temporal AB response to COVID-19 vaccination across 7 dialysis clinics in MA.

Results: Of 111 patients on PD in our center, 64 (58%) received COVID-19 vaccine as of April 2021 and had AB levels checked. A total of 60/64 (94%) of patients had a positive AB response and 4/6 (6%) did not mount a response. IgG levels in positive responders were a median of 11.5 (interquartile range, 1.9 – 20). Lower Kt/V was associated with a positive AB response (p = 0.045) and type of vaccine was associated with an AB response (p = 0.026). Age, BMI, diabetes, hypertension, lymphocyte count, or residual Kt/V were not statistically significantly associated with AB response to the vaccine (Table 1).

Conclusion: In conclusion, the vast majority of patients on PD developed positive AB response to the COVID-19 vaccine. While a small sample size limited statistical power, our results show promising COVID-19 vaccine effectiveness among patients on PD.
PO0141

Extremely Low Humoral Immune Responses to BNT162b2 Vaccine in Nursing Home Residents Undergoing Hemodialysis

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Background: As coronavirus disease 2019 (COVID-19) can cause lethal outcomes in hemodialysis (HD) patients, they should be protected effectively by vaccination. HD patients are known to have a weak immune response to vaccines, and the seropositive rate three weeks after first vaccination (BNT162b2 Pfizer) is around 35%. However, its efficacy among elderly HD patients remains unknown. We aimed to evaluate spike antibody levels of nursing home residents on long-term maintenance HD after the BNT162b2 vaccine, comparing those of healthy care workers.

Methods: Between April and May 2021, HD patients from a nursing home (nursing home group) and health care workers (the control group) who received BNT162b2 were included. Those with a prior history of COVID-19 were excluded. IgG anti-spike against COVID-19 were measured by Elecsys Roche (cut off index <1.0) 3 weeks after the first injection.

Results: The study included 27 nursing home residents on HD and 191 care workers, and 2 care workers were excluded due to a prior history of COVID-19. The nursing home group were 84.9 years old and 41% male, and the median of HD vintage was 51 months (IQR 28-119), and the control group were 45±14 years old and 29% male. Only 6 patients in the nursing group were confirmed as seropositive (22%), whereas the rate of responder in the control group was 99% (p<0.001). Notably, the IgG levels of 20 patients in the nursing home group were under the detectable level (<0.4). In contrast, the median of the IgG levels in the control group was 42 (IQR 18-87). Moreover, the prevalence of adverse reactions, such as developing fever, in the nursing home group was low compared to the control group (p<0.001).

Conclusions: The seropositive rate after BNT162b2 in elderly HD patients was quite low owing to poor immune responses. To prevent a COVID-19 outbreak in nursing homes, IgG levels against COVID-19 in elderly residents on HD should be paid attention to.

PO0144

Immunogenic Response of Hemodialysis Patients to COVID-19 Vaccine: A Multicenter Study

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Background: The use of the mRNA-based vaccine BNT162b2 against COVID-19 has shown great success preventing SARS-CoV-2 infection in the general population. Limited data exist regarding its effectiveness in patients requiring dialysis. Dialysis patients have reduced immune response following different types of vaccines including Hepatitis B vaccine. We aimed to assess humoral response and the factors associated with it in a large and diverse maintenance hemodialysis (MHD) patient population.

Methods: SARS-CoV-2 Anti-spike, anti-nucleocapsid and neutralizing antibody (Ab) levels of 424 MHD patients from 13 nationally spread dialysis units in Israel were compared with 155 control subjects (dialysis patients’ family members and dialysis units health care workers). Patients’ history, dialysis treatment details and Hepatitis B Ab (HBsAb) levels were obtained from dialysis units medical records.

Results: Our study included 400 MHD patients and 141 controls (58% males, 42% females), excluding 24 MHD and 14 control samples from anti-N positive cases, signifying previous SARS-CoV-2 infection. Anti-S antibodies developed in 89.3% of MHD patients and 99.3% of controls, (p<0.01) after a median time of 82 and 89 days from second vaccine dose for MHD and controls, respectively. Median anti-S titer was significantly lower in MHD patients compared with controls (median 194, IQR 118-242 vs. 69, IQR 33-119), and the control group were 45±9 years old and 41% male, and the median of HD vintage was 51 months (IQR 28-119), and the control group were 45±14 years old and 29% male. Only 6 patients in the nursing group were confirmed as seropositive (22%), whereas the rate of responder in the control group was 99% (p<0.001). Notably, the IgG levels of 20 patients in the nursing home group were under the detectable level (<0.4). In contrast, the median of the IgG levels in the control group was 42 (IQR 18-87). Moreover, the prevalence of adverse reactions, such as developing fever, in the nursing home group was low compared to the control group (p<0.001).

Conclusions: The seropositive rate after BNT162b2 in elderly HD patients was quite low owing to poor immune responses. To prevent a COVID-19 outbreak in nursing homes, IgG levels against COVID-19 in elderly residents on HD should be paid attention to.
Discussion: SARS-CoV-19 AB was measured longitudinally in this elderly HD population as a surrogate to the spike protein was negative 4 weeks after receiving a viral vector-based SARS-CoV-19 vaccine. He was relatively immunocompetent based on prior AB response to Hepatitis B vaccination. He became SARS-CoV-19 AB (+) 2.5 weeks after mild COVID-19 infection. Most studies on SARS-CoV-19 vaccination in ESKD have focused on mRNA vaccines, which show a reasonably high AB conversion rate after the second injection. We do not know if lack of detectable spike protein AB after vaccination necessarily precludes resistance to infection, nor do we know if this patient’s eventual seroconversion was due only to his COVID-19 infection or simply a slow response to the vaccine. There is evidence in the general public that efficacy of the viral vector-based SARS-CoV-19 vaccine may be lower than that of mRNA vaccines. With ESKD patients more susceptible to infection and less able to mount AB’s to vaccines, this case supports the use of mRNA SARS-CoV-19 vaccines preferentially in the ESKD population if AB seroconversion is the targeted intermediary outcome.

ESKD Immunoglobulin Response at 3 Months Post COVID-19 Vaccination
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Background: End stage kidney disease (ESKD) patients (pts) remain at high risk for COVID 19 infection. Inadequate post infection antibody response is reported in 10-11% of pts. Current data is limited on ESKD post vaccination (vac) 1 We report 3-month (mo) post vac response of ESKD pts receiving 2 doses of either Moderna or Pfizer vaccines.

Methods: Twenty- six of 42 stable ESKD pts completed 2 doses of either Moderna or Pfizer’s vaccine at Salem VAMC or at their nursing home facility during mo 01/02- 2021. 17/42 were not vaccinated (7 declined, 2 with COVID 19 infection, 6 acutely hospitalized) during that time. Antibody immune response testing using ADVIA Centaur COV2G automated 2-step sandwich immunoassay using indirect chemiluminescent technology and designed to detect the SARS-CoV-2 surface spike protein receptor binding domain (S1RBD) was completed in 05/2021. Measures obtained included reactivity to total SARS CoV-ab (IgM+ IgG) and IgG separately.

Results: Please see table 1 for results

Conclusions: ESKD vaccine response to COVID 19 after 3months was 96% for total immunoglobulin response (IgM and IgG) and 87.5% for total IgG antibody response compared to no reactivity in those nonvaccinated patients. Age and presence of diabetes did not significantly affect immune response. Approximately 12.5% of patients had nonreactive to IgG antibody after 3 months. Patients not developing an IgG response by 3 mo were found to have underlying immunosuppressive disease. ESKD with COVID 19 infection maintained IgG reactive response 3 months after active disease. Nonreactivity was seen in those neither infected nor vaccinated, suggesting that these patients have likely not been exposed to COVID 19 viral infection.

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PO0149
Durability of SARS-CoV-2 Spike Antibody Levels in Dialysis Patients After COVID-19 Infection
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Background: Durability of SARS-CoV-2 receptor-binding domain spike antibody (RBD s-Ab) levels among patients receiving dialysis after COVID-19 [WDE1] is unknown beyond 6 months. We describe the persistence (index value ≥ 1 and ≥ 2 U/L) of semi-quantitative RBD s-Ab levels in dialysis patients over 14 month period.

Methods: All maintenance dialysis patients (≥18 years old) within Dialysis Clinic, Inc. 260 clinics in 28 states with COVID-19 infection history and RBD s-Ab levels determined between Jan 1 and May 23, 2021 were included. On the day of RBD s-Ab level determination, patient demographics (age, sex, race, modality, ESKD vintage) and days since COVID-19 diagnosis were determined. Patient RBD s-Ab levels after COVID-19 vaccination were excluded.

Results: A total of 515 patients, mean age 62±14 years, 57% male, 46% White, 94% HD and vintage 4.6±4.4 years [EL1]. [HJM2] had 835 RBD s-Ab levels assessed at a median of 59 days (range 0-422 days) post COVID-19 infection. RBD s-Ab levels were assessed 1, 2 or ≥3 times in 64%, 18% and 18% patients, respectively. Only 32 (6.2%) patients had undetectable RBD s-Ab on the last draw. A cross sectional summary of the last available RBD s-Ab levels suggests that titers remain detectable for long duration (Figure[EL3] [HJM4]). In patients (N=186; 36%) with multiple RBD s-Ab levels (mean ≥ 18±15; median 28 days between levels), subsequent values were higher, lower [EL5] [HJM6] or unchanged 7%, 16% and 77% of time[EL7], respectively.

Conclusions: Most maintenance dialysis patients sampled developed SARS-CoV-2 RBD s-Ab after COVID diagnosis, and durability extends up to 14 months. Further elucidation of longitudinal RBD s-Ab values post-COVID-19 infection as well as after completing vaccination for SARS-CoV-2 is needed.

PO0148
The SARS-CoV-2 Vaccine Response in ANCA-Associated Vasculitis
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Background: The development of efficacious vaccines against COVID-19 is an overarching achievement of modern medicine. This efficacy, however, may not be achieved in patients on immunosuppression. We looked to ascertain humoral response and tolerability of these vaccines in patients with ANCA associated vasculitis(AAV) treated with B-cell depleting agents.

Methods: AAV patients who completed 2 doses of BNT162b2 or mRNA-1273 or a dose of JNJ-78436735, subsequently screened for spike protein antibody against SARS-CoV-2 were included in the study. Clinical details, demographics and immunosuppression regimes were ascertained, with primary outcome being humoral response to SARS-CoV-2. Statistics included Fischer’s exact test and Wilcoxon rank sum test.

Results: Forty-eight patients with a mean age of 67 (35% female) completed vaccine series with BNT1612b2(n=19), mRNA-1273(n=25) and JNJ-78436735(n=4). Vaccine associated side effects occurred in 27% of patients after 1st dose, with 39% after the 2nd dose. Spike protein antibody was tested at a median of 31 days after vaccination. 30(61%) patients had demonstrable antibody. All patients (n=44) other than post-transplant patients, were treated with Rituximab- only 17(44.3%) developed an antibody response. In the setting of rituximab treatment, absence of seroconversion post vaccination was associated with vaccine type, duration elapsed since last rituximab dose (figure 1), low IgM level and absence of B-cell reconstitution (all stastically significant). Two patients without serologic response had severe COVID-19 infection

Conclusions: This data demonstrates that majority of patients treated with rituximab lack demonstrable serologic response, with risk of severe COVID-19 infections despite vaccination. Confirmation of B-cell reconstitution before vaccination may have a bearing on serological conversion. It is imperative that authorities consider these factors while designing vaccination schedules and provide recommendations for booster doses in this vulnerable population.
Five-Month Impact of Tozinameran (BNT162b2) Vaccine on Kidney Transplant and Dialysis Patients: Serology and Clinical Outcomes
Michal Dranitzki Elhalal,1,2 Keren Tzakert,1,2 Iris Mor yose'f lev,1,2 Ido Burstein,3,2 Hadass Pri Chen,1,2 Younatan Oster,1,2 Dana G. Wolf,1,2 Idlo Z. Ben-Dor,1,2 Hadassah Hebrew University Medical Center, Department of Nephrology and Hypertension, Jerusalem, Israel; 4Faculty of Medicine, Hebrew University, Jerusalem, Israel; 5Hadassah Hebrew University Medical Center, Department of Clinical Microbiology and Infectious Diseases, Jerusalem, Israel.

Background: Dialysis-treated (DT) and kidney transplant (TX) patients face higher morbidity and mortality risks than the general population during COVID-19 pandemic.Determining humoral response and associated COVID-19 morbidity after vaccination will guide risk assessment and changes in vaccination policy in this vulnerable population.

Methods: Prospective cohort study up to 5 months follow-up after Tozinameran or SARS-CoV-2 vaccine infection. Primary outcomes: qualitative and quantitative anti-S1/ S2 antibody (Abs) and disease rates during follow up. Anti-SARS-2 IgG Abs were quantified using LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin) immunoassay in serum of TX, DT and treating team at our hospital. Demographics and clinical data were collected from participants files.

Results: 174 DT patients (40% women, age 65±15 years) 253 TX patients (33%, 53±14 years) and 71 control participants (65%, 44±14 years) were recruited. 3 months or more after vaccination we detected anti S1/S2 ABs in 81% of DT (95%CI, 72-90%), 43% of TX (95%CI, 29-57%) and 100% of controls. After COVID-19 respective rates were 94% (95%CI, 83-100%), 75% (95%CI, 60-90%) and 100%. Quantitative titers were in line with qualitative ones. Predictors of negative serology were older age, diabetes, cancer history, lower lymphocyte count and lower vitamin D. Peritoneal dialysis predicted higher titers compared to hemodialysis. In TX, hypertension and higher levels of immunosuppression predicted lower titers. Vaccination was associated with fewer subsequent COVID-19 infections (HR=0.23, 95%CI 0.05-0.99, p=0.05). Higher antibody titers associated with fewer events, HR 0.41/unit increase in log., titer (p<0.05).

Conclusions: Patients with ESRD, particularly TX, mounted delayed and diminished antibody response to vaccination, and lesser response was associated with more infections. Thus, measures to protect non-responsive patients are urgently required.

PO0150
COVID-19 Vaccine and Multiple Viral Infection: Cross-Reaction?
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Introduction: The COVID-19 pandemic has brought a lot of challenges in the medical and educational field. Every day, new facts and knowledge are published about the pathophysiology, treatment, and prognosis of COVID-19 patients. In addition, community response to vaccination and vaccine side effects has been one of the major talking points in social media. The general public wants to fully understand if the vaccine really provides immunity and possible side effects of its use.

Case Description: Under this premise, a 36 y/o female patient with a past medical history of type 2 diabetes mellitus, hypertension and obesity came to emergency department 2 days after she received the second dose of Moderna COVID-19 vaccine and developed non-quantified fever, general malaise, vomiting and watery diarrhea. Associated symptoms were scattered non-blanching maculopapular rash from head to shoulders to mid back and abdomen, pastes in ear and decrease urine output. Patient was unable to urinate for at least 48hrs. Laboratory bloodwork was remarkable for hyponatremia, hypochloremia, high anion gap metabolic acidosis and creatinine clearance of 18ml/min. Hepatic enzymes were more than five times elevated, and total bilirubin was elevated as well. Urinalysis reported proteinuria, positive leukocytes esterase, few calcium oxalate crystals and many urate amorphous sediment. Patient was convinced that symptoms were related to COVID-19 vaccination. Etiology of symptoms remained unclear at admission, for that reason she was admitted and received isotonic hydration, clearly suggest pre-renal injury. Viral infection in this patient. From dehydration to sepsis is the spectrum of differential diagnosis in this patient. The renal function recovery after hydration, could be the primary reason of her dehydration. However, the event of vaccination, could not be completely ruled out. Was the vaccine a catalyst for viral infection? Or was the patient a confounder in this patient’s renal failure?

PO0152
Antibody Response Post SARS-CoV-2 Vaccination in Kidney Transplant Recipients
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Background: This project aims to analyze the proportion of patients who did not develop antibodies following COVID-19 vaccination and to ensure that the immune stimulation secondary to the vaccine is not associated with clinical rejection and DSA development.

Methods: Samples collected from COVID-19 vaccinated kidney transplant recipients from 3/1/21-4/26/21 were tested for DSA and COVID-19 antibodies using a multi-antigen detection Luminex platform (BioRad). The following were tested: receptor binding domain IgG, spike 1 IgG, spike 2 IgG, nucleocapsid IgG.

Results: 94 patients were included in this study. 57% had no antibodies post second dose of COVID-19 vaccination. This number decreased to 52% when looking at samples collected 2-2 weeks after the final vaccine dose. Of all positive patients, 19% showed evidence of previous COVID-19 infection based on nucleocapsid positivity, which excluded from the cohort analysis, to lead a higher rate of patients not responding to the vaccine. We did not observe a correlation between antibody positivity and demographics or clinical characteristics. Only 2 patients developed new DSA post-vaccination, which 5 had positive antibodies with an average decrease of 17 U/mL for S1 IgG per week.

Conclusions: When excluding patients previously infected with COVID-19, the rate of positive antibody formation post vaccine is 35%. More research needs to be done to understand the correlation of antibody response and protection against COVID-19 infection.
PO0153

Comparison of Safety and Outcomes Related to Remdesivir Use Among Dialysis Patients Hospitalized with COVID-19


Background: Use of remdesivir in the treatment of dialysis patients with Coronavirus Disease 2019 (COVID-19) has been limited due to inconclusive data regarding safety outcomes among patients with severe renal impairment. For this reason, the FDA has not recommended remdesivir use in patients with eGFR < 30 ml/min per 1.73 m². We sought to evaluate outcomes among dialysis patients with COVID-19 who received remdesivir in a real-world setting.

Methods: We conducted a retrospective study of patients on hemodialysis or peritoneal dialysis hospitalized with COVID-19 between 5/1/2020 - 1/31/2021 within the integrated health system of Kaiser Permanente Southern California. Patients with a COVID-19 International Classification of Diseases (ICD)-10 code: U07.1 and laboratory confirmed SARS-CoV-2 infection within 14 days prior to admission date to two days after admission date were included. The primary endpoint was 30-day all-cause mortality. Secondary endpoints were intensive care unit (ICU) stay, and evidence of acute liver injury defined as AST and/or ALT values >5x upper limit of normal.

Results: A total of 486 patients (407 hemodialysis and 79 peritoneal dialysis) met inclusion criteria. Among these, 112 patients (23%) were treated with remdesivir, with median treatment time of 4 days (IQR: 2-5). Mean age was 63.8 years with 63.8% male and 63.0% Hispanic patients. There were 80.2% of patients who received treatment with steroids during hospitalization. Relative risk (RR) for all-cause 30-day mortality was 0.74 (95% CI, 0.52-1.05) in remdesivir treated patients compared to untreated patients. Acute liver injury occurred in 1.8% and 2.4% of remdesivir treated and untreated patients, respectively. ICU admissions occurred in 14.3% of remdesivir treated and 16% of untreated patients.

Conclusions: Among dialysis patients hospitalized with COVID-19, treatment with remdesivir was not associated with worse outcomes in terms of liver injury or ICU admission, and demonstrated a trend (26% lower risk) toward decrease in 30-day mortality, though no statistical significance was found due to insufficient power.

PO0154

Outcomes Associated with Tocilizumab Use in Patients with COVID-19: Vaccines, Diagnosis, and Treatment


Background: The percentage of critically ill amongst COVID-19 infected patients stands at 5%. The incidence of acute kidney injury in those patients varies according to risk factors. A little is known about the use of Tocilizumab in patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: This is a retrospective study of 22 COVID-19 patients. Patients were between 18 and 80 years old, had proven COVID-19 infection, were admitted to the ICU between April 1 and July 15, 2020, received CRRT and Tocilizumab parenterally. Other therapies included antivirals, hydroxychloroquine and convalescent plasma. We included biochemical outcomes related to cytokine storm as well as clinical outcomes; Those included ventilator dependence, renal outcomes, length of hospital stay and mortality.

Results: 21 out of 22 patients were males. Median age was 56 years. 14 patients had hypertension and 13 had diabetes mellitus. All patients had cytokine storm on admission (elevated IL-6 and CRP levels). At the completion of the follow up (average 44.4 days), 20 out of 22 patients experienced improvement in IL-6 and CRP levels. 11 patients died. 13 experienced improvement in oxygen requirements including 9 who were successfully extubated. 13 were still on CRRT (including 10 patients who died) while 9 patients became dialysis independent (5 had complete recovery of kidney function and 4 developed chronic kidney disease). There was no reported side effect from using tocilizumab.

Conclusions: Tocilizumab can be considered in critically ill COVID-19 patients with severe AKI and cytokine storm. No dose adjustment is needed in patients on CRRT. Further studies are required to confirm our results.
On 16 Apr 2021, the EUA was revoked over concerns of resistance among SARS-CoV-2 variants. Between 01 Jan and 16 April 2021, physicians at DaVita dialysis clinics were able to order bamlanivimab (700 mg) treatment during dialysis for nonhospitalized hemodialysis patients who tested positive for SARS-CoV-2 infection and met the eligibility criteria. Here, we report safety data among dialysis patients who received bamlanivimab as a monotherapy for COVID-19.

Methods: Bamlanivimab was administered intravenously as a single dose over the course of 60 minutes during a regularly scheduled hemodialysis session. All patients were monitored for at least 1 hour after bamlanivimab administration. All facilities were required to have emergency medications on-site, and staff were trained to identify and treat potential reactions. A serious adverse event was considered if a patient developed anaphylaxis or any condition requiring use of an epinephrine injection (1:10,000 IM) or albuterol, was sent to the emergency department, or was hospitalized after bamlanivimab administration. An adverse event was considered if a patient developed fever, chills, hives, rash, hypotension, headache, nausea, fatigue, dizziness, angioedema, muscle pain, or throat irritation.

Results: 264 patients with newly diagnosed SARS-CoV-2 infections received a single dose of bamlanivimab at DaVita. Among all patients who received the drug, 46% were women and the mean age was 60 years. On average, patients were followed for 64 days postinfusion. There were 0 adverse events or serious adverse events documented in the 1-hour postadministration observation window.

Conclusions: Bamlanivimab was found to be safe in dialysis patients.

PO0156
Intravenous Immunoglobulin: Answer to COVID-19?

Introduction: Traditionally intravenous immunoglobulin (IVIG) has been used for immunodeficiency disorders. It has been also used in certain autoimmune and infectious diseases. IVIG has several immunomodulatory and anti-inflammatory effects. Here, we are reporting a case where IVIG was used for BK viremia in a patient with COVID-19 pneumonia who showed dramatic recovery of COVID-19 symptoms and laboratory parameters.

Case Description: Our patient is a 55-year-old African American male who received simultaneous pancreas and kidney transplant in April 2019 with induction immunosuppression with thymoglobulin and was on chronic immunosuppression with tacrolimus and mycophenolate mofetil. His post-transplant course was complicated by BK viremia and presumed BK nephropathy after 2 months. His immunosuppression was gradually tapered off but his viremia was persistent despite being off mycophenolate and low target goal of tacrolimus. Patient partially responded to high dose IVIG so we decided to continue monthly high dose IVIG with daily Leulimumide. Later in April 2021, patient was admitted with COVID-19 symptoms with normal oxygen saturation at room air. His clinical condition worsened over the following 4-5 days in the form of hypoxic respiratory failure requiring high flow oxygen supplements and Acute Kidney injury (AKI) with nephrotic range proteinuria and gradual rising inflammatory markers. Patient was about to be transferred to the Intensive Care Unit as his clinical condition was worsening and refractory to the traditional treatment with steroid and antibiotics. On day 10 he received his monthly dose of IVIG therapy (0.5 g/kg body weight for 4 consecutive days). His COVID symptoms started to improve from day 2 of the treatment. His inflammatory markers were dramatically down trended over the next 3-4 days post IVIG. He was discharged home with oxygen therapy (3L/min) by the day 5 post treatment with IVIG with recovering AKI.

Discussion: Few international studies have reported that initiation of high dose IVIG as adjuvant treatment for COVID-19 disease in selected patients may result in early clinical and laboratory recovery. The studies are limited due to the small sample size and patient selection criteria. Although our patient exhibited dramatic recovery, randomized clinical trial needs to be done to explore more about effect on COVID-19 pneumonia and COVID-19 associated AKI.

PO0157
CytoResp, or CytoSorb for COVID-19 Patients with Vasoplegic Shock: A Prospective Randomized Pilot Study
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Background: Several observations indicate a hyperinflammatory state in severely ill COVID-19 patients as target for therapeutic interventions. The aim of this study was to investigate the effect of extracorporeal cytokine elimination by CytoSorb on COVID-19 associated vasoplegic shock.

Methods: In this prospective randomized pilotstudy patients with vasoplegic shock requiring norepinephrine >0.2 µg/kg/min, CRP >100 mg/L and indication for kidney replacement therapy were randomized 1:1 to receive CytoSorb treatment for 3-7 days or standard of care. The primary endpoint was time until resolution of vasoplegic shock (futility of vasopressor therapy for at least 8 hours to sustain a MAP ≥65 mmHg). Data were analyzed using Cox-regression and Kaplan-Meier curves.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO0158
CRRT with the oXiris Filter Attenuates IL-6 in a Patient with Severe COVID-19
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Introduction: SARS-CoV-2 infection can result in ARDS and multiorgan dysfunction. The pathophysiology underlying Covid-19 includes a hypercoagulable state and a cytokine release storm with upregulation of IL-6, IL-10, and TNF-alpha, which are associated with ICU admission, ARDS, AKI, and increased mortality. While there are no proven treatments for this cytokine storm, tocilizumab, has shown promise in studies against severe Covid-19, suggesting that cytokine removal via blood purification products like oXiris may help achieve immune homeostasis.

Case Description: A 70-year-old male status post DDRT in 2016 presented with fevers, malaise, and dyspnea. He tested positive for SARS-CoV-2 and was admitted to the ICU on 12/23/2020 with worsening and refractory acute respiratory distress syndrome requiring high-flow nasal cannula with a rate of 50L/min and FiO2 of 90%. Urinalysis revealed pyuria, hematuria, and proteinuria. Labs revealed a creatinine of 2.4 and a BUN of 61 as well as a CRP of 130, ESR of 65, D-dimer of 1048, LDH of 325, ferritin of 3891, and IL-6 of 5.6 consistent with severe Covid-19. An ultrasound of his allograft kidney was normal. The patient then went into PEA arrest and was intubated with decreasing urine output, therefore, was initiated on CRRT with an oXiris filter for 48 hours followed by a M150 filter. His P/F ratio increased and his IL-6 and SOFA score decreased while on the oXiris filter, however both CRP and LDH increased. After switching filters, the patient’s P/F ratio quickly declined with a rapid increase of IL-6. Ultimately, the family decided to withdraw care.

Discussion: The oXiris filter could potentially manage the cytokine storm seen in Covid-19 as it is the only filter shown to remove cytokine and endotoxins, improve renal function, and have antithrombogenic properties as it is grafted with heparin. It is an AN69-based oXiris membrane treated on the inside with a high concentration of polyethyleneimine (PEI) binding cytokines and endotoxins. Given the impact of Covid-19, more studies must be done to assess if oXiris may serve as an effective treatment.
Blood Purification in a Critically Ill COVID-19 Patient with Cytokine Storm: A Case Report

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Introduction: Cytokine storm syndrome (CSS) is a common and severe cause of mortality among critically ill COVID-19 patients. BPTs, especially continuous renal replacement therapy (CRRT), may work by removing cytokines and blocking the cascade of inflammation and thus preventing the progression of CSS. However, the efficacy of Blood purification therapies (BPTs) in patients with complications of CSS but without AKI (acute kidney injury) is still controversial.

Case Description: We report the case of a 66-year-old female who had severe COVID-19 pneumonia without AKI. After admission, the patient’s condition progressed rapidly to severe respiratory failure and heart failure, and she had been treated with venous-venous extracorporeal membrane oxygenation (VV-ECMO). Meanwhile, the level of interleukin-6 (IL-6) increased rapidly and reached 304.8 pg/ml. Although there was no kidney injury, CRRT was initiated to reduce the levels of cytokines in circulation, while the decrease in IL-6 serum and dialysate was not significant. Oxiris-CRRT was then introduced and there was a significant decrease in serum levels of IL-6 after 9 sessions of Oxiris-CRRT and two sessions of TPE. However, when we stopped Oxiris-CRRT after the third treatment, the serum levels of IL-6 were elevated again 12 hours after the suspension of Oxiris-CRRT. Subsequently, the patient received 6 additional Oxiris-CRRT sessions until the serum IL-6 levels of 2.67 pg/ml. After 144 days of hospitalization, including 2 CRRT sessions, 9 Oxiris-CRRT sessions and 2 therapeutic plasma exchange (TPE) sessions, she completely recovered (shown in Fig. 1).

Discussion: In our patient, BPTs, especially Oxiris-CRRT, showed unique superiority and application value in the clearance of excess plasma cytokines, promoting a smooth recovery, which suggests that even if AKI does not occur, it is beneficial to use BPTs to prevent the progression of CSS in COVID-19 patients.

Results: IL-6 levels gradually decreased to normal levels after 9 sessions of Oxiris-CRRT and two sessions of TPE.

COVID-19 vs. Bloodstream Purification: A Targeted Therapy

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Background: The use of bloodstream purification has been well studied in bacteremia but the emergence of COVID found a new target. Using blood purification in the fight against COVID we have found a potential treatment for viremia and pneumonia, cytokine storm and decompensation, and superinfections in COVID. When used at the appropriate time, blood purification has the potential to prevent further organ injury.

Methods: The following case series is an individual clinical observation of patients with COVID-19 and potential for bloodstream purification.

Results: 28M w/o significant PMHs, transferred to BAMC for ECMO due to severe COVID. He initially improved, but decompensated with MRSA bacteremia, ECMO/CRRT and quadropause dependent. He was treated with the Seraph for bloodstream purification and was off all vasoeditors within 6 hours. He recovered, and was ultimately discharged without distressing ECLS depdence. 64 M w/ CAD and CKD was admitted for mild COVID pneumonia requiring minimal o2. On hospital day 9-11 he decompensated ultimately requiring intubation and vasoeditor support with AKI and oliguria. He was treated with the Seraph for 16 hours and was off vasoeditors within 16 hours, urine output recovered within 24 hours, he was extubated in 48 hours and discharged from the ICU after 96 hours. 52 M w/ CKD/COPD/CHF/CAD admitted for mild COVID PNA, decompensated on day 12, required intubation / vasoeditor support / CRRT, treated for 24 hours on CRRT with no further improvements and was off all vasoeditors within 24 hours. 64 M w/ CKD/CHF/CAD admitted for NSTEMI and cardiac shock, found to be non-obstructive and likely viral cardiomyopathy due to COVID. He was started on dobutamine / levophed and IABP. Due to oliguria he was treated with CRRT and Seraph for blood purification. Within hours he was off vasoeditors, no longer needing IABP after 24 hours, and ultimately recovered renal function within 48 hours.

Conclusions: While further study is needed, the use of blood purification for specific targets in COVID appears to have incredible benefits. Due to documented pathogen removal impairment in vivo (patient), we did not consider BPTs to be a useful or beneficial treatment for any bloodstream infections, but especially in the susceptible COVID population it seems to have miraculous benefit. The Seraph also appears to mitigate organ injury from the cytokine storm caused by COVID due to attenuation of the cytokine storm.

PO0161

Hemoperfusion with Seraph® Filter Late in the Course of Severe COVID-19 Pneumonia

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Introduction: Severe COVID-19 infection is often associated with uncontrolled cytokine response and a milieu of circulating inflammatory markers. Cytokine adsorption with viral binding of SARS-CoV-2 has been utilized in severe COVID-19 cases under emergency use authorization by the FDA. Evaluating observations of its use showed reduction in inflammatory markers; improvement in hemodynamics; reduction of vasopressor requirements and oxygen support; and avoidance or reduction of time on mechanical ventilation. We report a case of hemoperfusion utilizing the Seraph® filter as a last resource in a patient with life-threatening COVID-19 infection.

Case Description: A 37-year old female with a diagnosis of morbid obesity (BMI 60 kg/m2) presented to the University of Kentucky hospital with acute respiratory failure from COVID-19 pneumonia. The patient required ICU care, mechanical ventilation and eventually extracorporeal mechanical oxygenation (ECMO) on day 5 of her hospital stay. Despite aggressive COVID-19 management, her condition gradually worsened. On day 15 of her hospital stay, extracorporeal sorbent hemoperfusion via Seraph® filter was delivered through PrismaFlex® in tandem with the ECMO circuit. Her serum IL-6 levels dropped from 154 pg/ml to 29 pg/ml, and C-reactive protein from 317 mg/l to 294 mg/l within 2 hours of treatment completion. She had intermittent fevers up to 40°C, especially in the 48 hours prior to treatment which resolved right away with hemoperfusion and she remained afebrile for the next 72 hours. There was, however, no significant change in her hemodynamics and overall clinical status and the patient remains on ECMO and mechanical ventilation at the time of this report (Day 34).

Discussion: This case exemplifies that hemoperfusion therapy delivered late in the course of severe COVID-19 disease is still effective in decreasing circulating inflammatory markers, but may not be effective in significantly and positively affecting clinical outcomes. Although circulating inflammatory markers could be used to guide eligibility for hemoperfusion therapy, timing of hemoperfusion should be considered in clinical trials to effectively test the potential of this intervention to ameliorate clinical outcomes in susceptible populations.
situates a multi-level inflammatory syndrome in some of the most critically ill patients with overlapping features of other hyperinflammatory or autoimmune diseases. Thus, plasma exchange (PE) has become a subject of controversy as potential therapy in these patients. Here, we report the results of the so far largest cohort of critically ill COVID-19 patients treated with PE.

**Methods:** All critically ill COVID-19 patients treated with PE at Heidelberg University Hospital were analyzed between April and December 2020. Disease course and outcomes were compared with a standard care control group matched for age, sex, and disease severity. Changes in laboratory and clinical parameters were studied longitudinally. Kaplan-Meier and Cox regression analyses were performed.

**Results:** In total, 28 critically ill COVID-19 patients were treated with an average of 3 PE procedures per patient. No relevant complications occurred during PE therapy. Inflammatory markers and biochemical indicators of end-organ damage and endothelial activation were significantly reduced during PE. These laboratory changes were accompanied by normalization of body temperature, improved pulmonary function, and reduced vasopressor demand. Most importantly, the laboratory and clinical improvements were maintained after the last PE. In contrast, most parameters in the control group did not improve significantly over seven days, although baseline clinical and laboratory parameters were comparable in both groups. Kaplan-Meier analysis showed improved 30-day survival in the PE group compared to the control group (67.9% vs. 42.9%, p=0.044). In a multivariable analysis, the hazard ratio for death was 0.27 (95% CI 0.11-0.68, p=0.005) with PE versus care.

**Conclusions:** Our data further suggest that PE represents a potential therapeutic strategy for a subset of severe COVID-19 cases. The observed PE-related effects appear to go beyond a purely artificial improvement in blood parameters and may indicate a reversal of the complex COVID-19 immunopathology. Randomized controlled trials are urgently needed.

**PO0164**

COVID-Related Renal Thrombotic Microangiopathy: Role of Plasma Exchange


**Introduction:** The most common COVID-19 associated glomerular diseases are COVID associated nephropathy (CINAV) and Thrombotic Microangiopathy (TMA). Other less common glomerular diseases associated with COVID reported are antineutrophil cytoplasmatic antibody (ANCA) vasculitis, anti-glomerular basement membrane (Anti GBM) antibody disease, podocytopathies, and IgA nephropathy. We report a case of TMA due to COVID-19 infection.

**Case Description:** A 67-year-old woman with asthma was admitted for COVID related respiratory failure and was noted to have acute kidney injury with anemia and thrombocytopenia. She was hypertensive and urine analysis was notable for hematuria and proteinuria. ANA, ANCA, Anti GBM, Coombs, ADAMTS13, disseminated intravascular coagulation panel, serum immune fixation and free light chains, cryoglobulins, and infectious work up were unrevealing. Complement C3 and C4 were low, lactate dehydrogenase and bilirubin were high, haptoglobin was undetectable, and schistocytes were seen on peripheral smear which raised concern for thrombotic microangiopathy. Renal function deteriorated rapidly with ensuing anuria prompting initiation of dialysis. Kidney biopsy confirmed acute thrombotic microangiopathy. She was started on plasma exchange (PLEX) for COVID related thrombotic microangiopathy and she started producing urine with rapid improvement in creatinine (Cr) after two treatments. Cr was down to 3.11mg/dL from a peak of 7.45 mg/dL after PLEX and normalized at discharge. The patient is currently being monitored with renal panel and complete blood picture every three months, as an outpatient.

**Discussion:** COVID is known to cause TMA that is presumed to be secondary to endothelial dysfunction and complement activation. There are no standard guidelines for treatment. Terminal complement blockade was not used in our patient. Our case demonstrates the efficacy of PLEX in the treatment of COVID related TMA. Early recognition and treatment is crucial and may reduce morbidity and mortality.

**PO0165**

Sustained Low-Efficiency Dialysis: Continuous Renal Replacement Therapy in Critical Care: COVID-19 Patients

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**Background:** Acute kidney injury among patients with COVID-19 infection is a poor prognostic indicator. There is limited evidence to guide the nephrology community if there are any risk or advantages of using sustained low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT). We aim to evaluate the clinical outcomes of COVID-19 patients receiving renal replacement therapy in the intensive care unit (ICU).

**Methods:** This is a retrospective chart review of adult patients with COVID-19 admitted to ICU in the state of Qatar who had 1)acute kidney injury and 2)received renal replacement therapy between February to August of 2020. We evaluated clinical characteristic, severity of illness, mortality, and renal outcomes at 30 days.

**Results:** Among 127 patients with acute kidney injury requiring dialysis in ICU, 16 patients were on CRRT, 68 patients were on SLED, and 43 patients were on both SLED and CRRT. We did not observe significant difference among age, gender, ethnicity or baseline creatinine. Most common indication for indication of dialysis was volume overload followed by acidosis in all groups with serum creatinine of 264umol/L vs 499umol/L vs 351umol/L in CRRT, SLED, and CRRT+SLED, respectively. Inflammatory markers, Proinflammatory requirement and APACHE II score were similar among all groups. 30-day Survival was 23%, 50% and 9% and Among 34 patients on SLED who survived, 6 were dialysis dependent post COVID-19 infection.

**Conclusions:** Acute kidney failure in critically ill COVID-19 patients is associated with high mortality. A lower mortality, but high morbidity is observed in patients receiving SLED in critical care setting. Further investigation of SLED in COVID-19 should be considered.

**PO0166**

Detection of SARS-CoV-2 in Dialysis Effluent on a Peritoneal Dialysis Program in Mexico City: Four Cases


**Introduction:** Since the rapid spread of the COVID 19 pandemic, it is crucial to identify possible sources of transmission of the SARS-CoV-2 virus in order to perform proper infection control and safety. There has been interest to identify the presence of SARS-CoV-2 in different compartments including peritoneal compartment. SARS-CoV-2 was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in dialysis effluent on a few single cases while other authors have reported negative results. Peritoneal membrane pores have a diameter of 20-40 nm while the SARS-CoV-2 virion diameter is between 60 to 140 nm, theoretically the virion could reach the peritoneal cavity by hemogenous diffusion or through the dialysis catheter after contact contamination.

**Case Description:** We report dialysis effluent findings of four patients, two women and two men, with an age range of 35 to 64 years and different comorbidities including: diabetes mellitus, hypertension and obesity. They were diagnosed with COVID-19 using RT-PCR assay on nasopharyngeal samples or by tomography findings. RT-PCR samples of peritoneal effluent were obtained with a length of stay on peritoneal cavity of 6 hours, without centesis of the sample. Three patients were positive for presence of SARS-CoV-2 on nasopharyngeal sample and dialysis effluent, while the fourth patient was negative in both samples despite having tomography findings suggestive of COVID-19 infection. It should be noted that in the 3 patients that had a positive RT-PCR on both nasopharyngeal and peritoneal effluent, samples were obtained within the first 7 days following the onset of symptoms associated with COVID-19 and on the fourth patient the peritoneal effluent sample was obtained 12 days after initial symptoms. All patients presented with acellular peritoneal fluid. No abdominal symptoms were reported.

**Discussion:** Presence of SARS-CoV-2 on peritoneal fluid continues to be a subject of debate. Peritoneal effluent cultures have demonstrated: a degree of systemic hypercoagulability with unique features, including a procoagulant state, activated platelets, increased bleeding risk. Maintaining circuit patency and avoiding bleeding risk has become a priority. Data regarding anticoagulation in COVID-19 patients who received hemodialysis is limited. This study’s primary objective is to compare hemodialysis clotting rate in COVID-19 patients who received anticoagulant versus those without anticoagulant.

**Methods:** Retrospective chart review for all COVID-19 patients who received hemodialysis at Banner Medical Center Tucson Campus Between November 2020 and January 2021. Primary outcome was clotting rate during hemodialysis. CRRT was excluded.
PO0168

Divergence Between Serum Creatinine and Cystatin C in Estimating Glomerular Filtration Rate of Critically Ill COVID-19 Patients

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Background: The clinical use of serum creatinine (sCr) and Cystatin C (CysC) in kidney function evaluation of critically ill patients has been in continuous discussion. The values of estimated glomerular filtration rate calculated by sCr(eGFRcre) and CysC (eGFRcysc) of critically ill COVID-19 patients were investigated in this study.

Methods: This is a retrospective, single-center study of critically ill patients with COVID-19 admitted in Intensive Care Unit (ICU) at Wuhan, China. Control cases were moderate COVID-19 patients who were matched in age and sex at a ratio of 1:1. The eGFRcre and eGFRcysc were compared. The association between eGFR and death were analyzed in critically ill cases. The potential factors leading to the divergence between eGFRcre and eGFRcysc were explored.

Results: A total of 76 critically ill COVID-19 patients were concluded. The mean age was 64.5±9.3 years and the male : female ratio was 49:27. At ICU admission, their eGFRcre (85.45 (IQR 60.58-99.23) ml/min*1.732m²) were much higher than eGFRcysc (60.6 (IQR 34.75-79.06) ml/min*1.732m²). About 50% of them showed eGFRcysc < 60 ml/min/1.73 m2 while 25% showed eGFRcre < 60 ml/min/1.73 m2 (c2=10.133, P=0.001). This divergence was not observed in control group. The potential factors influencing the included serum interleukin-6 (IL-6) level, tumor necrosis factor(TNF-α) level as well as APACHEII. Reduced eGFRcre (<60 ml/min/1.73 m2) was associated with death(HR=1.939,95%CI 1.078-3.489, P=0.027).

Conclusions: The eGFRcre was higher than eGFRcysc in critically ill cases. The divergence might be affected by the inflammatory condition. Reduced eGFRcre predicted in-hospital death. In these patients, we advocate for caution when using eGFRcysc.

Funding: Private Foundation Support

PO0169

Serum Sodium and Patient Symptoms in COVID-19 Hospitalizations

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Background: Disorders of serum sodium (SNa) are common in hospitalized patients with COVID-19 and associated with longer length of stay and inpatient mortality. However, the association of SNa with patient-reported outcomes is not clear.

Methods: The Brigham and Women’s Hospital COVID-19 Registry is a prospective cohort study of consecutive, adult patients admitted with confirmed SARS-CoV-2 infection (n=809). We examined the association of SNa (continuous and tertiles) at admission with: 1) patient symptoms obtained from detailed chart review; and 2) in-hospital mortality using unadjusted and adjusted logistic regression models. Covariates included demographic data and comorbidities. Only index admissions were considered.

Results: Mean age was 60 years, 48% were male, and 35% had diabetes. The most frequent symptoms were cough (64%), fever (60%) and shortness of breath (46%). In adjusted models, higher SNa (per mmol/L) was associated with lower odds of GI symptoms (OR 0.96; 95%CI 0.93-0.99), higher odds of confusion (OR 1.08; 95%CI 1.40-1.13) and higher odds of in-hospital mortality (OR 1.06; 95%CI 1.02-1.11). Compared with the lowest tertile, the highest tertile of SNa was associated with a lower odds of GI symptoms and anosmia/ageusia, and higher odds of confusion and in-hospital mortality (Table 1).

Conclusions: In this prospective cohort study of hospitalized patients with COVID-19, hypernatremia is associated with higher odds of confusion and in-hospital mortality and lower risk of GI symptoms and anosmia. The presence of dysnatremia may help identify higher-risk patients with COVID-19 and prompt ascertainment of patient symptoms, both of which may improve patient-centered approaches to care.

Table 1

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>SNa Tertile 1</th>
<th>SNa Tertile 2</th>
<th>SNa Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI symptoms</td>
<td>REF</td>
<td>1.03</td>
<td>0.95</td>
</tr>
<tr>
<td>Confusion</td>
<td>REF</td>
<td>1.01</td>
<td>0.93</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>REF</td>
<td>1.06</td>
<td>0.99</td>
</tr>
</tbody>
</table>

PO0170

Lower CD3 and CD4 Counts in Kidney Transplant Recipients Who Did Not Respond to COVID-19 Vaccination


Background: Kidney transplant recipient’s response rate to COVID-19 vaccination is reportedly less than 54% after the 2nd dose, significantly lower than general population and dialysis patients, reported as between 85-90% and 95-100%, respectively.

Methods: We studied SARS-CoV-2 anti-spike IgG levels in our kidney transplant recipients after their COVID-19 vaccination using the OrthoV IgG platform.

Results: 69 kidney transplant recipients received a SARS-CoV-2 vaccine (47 Pfizer, 20 Moderna and 2 Johnson and Johnson) at a median 36 months after transplantation (range, 3 months to 22 years). 61% were male, 39% Black, 29% Hispanic with a median age of 60 (range 22-82). 72% were deceased-donor kidney transplant recipients. 23 patients had previous history of COVID-19 diagnosed by SARS-CoV-2 PCR and/or anti-nucleocapsid antibody and 21 of those patients (91%) developed anti-spike IgG after 1st or 2nd dose with a median level of 13.2 (11.2-16.2). 46 patients without history of previous COVID-19, 17 (37%) developed anti-spike IgG at a median of 28 days (range 10-72) after the second vaccine dose with a median level of 5.7 (1.22-15.4). Patients who didn’t develop anti-spike IgG tended to be older, of African-American descent, on MMF with augmented immunosuppression, lower T cell counts, African-American race and older age.

Conclusions: In summary, most kidney transplant recipients without history of COVID-19 did not produce anti-spike IgG after being fully vaccinated and it is associated with augmented immunosuppression, lower T cell counts, African-American race and older age.
PO0171
Prognostic Significance of Urinary Biomarkers in Patients Hospitalized with COVID-19

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Background: Acute kidney injury (AKI) is common in patients with COVID-19 and associated with poor outcomes. Urinary biomarkers have been associated with adverse kidney outcomes in other settings and may provide additional prognostic information in patients with COVID-19.

Methods: We evaluated 19 urinary biomarkers of injury, inflammation, and repair in patients hospitalized with COVID-19 at 2 academic medical centers between April and June 2020. We associated biomarkers with a primary composite outcome of KDIGO stage 3 AKI, requirement for dialysis, or death within 60 days of admission. We also compared various kidney biomarker levels in the setting of COVID-19 versus other common AKI settings.

Results: Out of 157 patients, 24 (15.3%) experienced the primary outcome. Two-fold higher levels of neutrophil gelatinase-associated lipocalin (NGAL) (HR: 1.53; 95% CI: 1.33-1.76), monocyte chemoattractant protein (MCP-1) (HR: 1.86; 95% CI: 1.48-2.33), and kidney injury molecule-1 (KIM-1) (HR: 2.33) were associated with highest risk of the primary outcome. Higher epidermal growth factor (EGF) levels were associated with a lower risk of the primary outcome (HR 0.52; 95% CI: 0.31-0.89). Urinary biomarkers were associated with poor outcomes. Urinary biomarkers have been associated with adverse kidney outcomes in other settings and may provide additional prognostic information in patients with COVID-19.

Conclusions: Urinary biomarkers are associated with severe kidney complications in patients with COVID-19 and provide valuable information to monitor kidney disease recovery and progression.

Funding: NIDDK Support

PO0172
Urinary Test Predicts Kidney Injury and Death in COVID-19

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Background: Kidney injury is a common feature of COVID-19 infection, but serum creatinine (Scr) is not a sensitive or specific marker of kidney injury. We hypothesized that measurement of molecular markers of tubular injury can diagnose COVID-19 associated kidney injury and predict a poor prognosis.

Methods: This is a prospective cohort study of 444 consecutive COVID-19 patients in a New York City Emergency Department recruited in March and April, 2020. Urine and blood were collected simultaneously at hospital admission (median time of day 0, IQR 0-2 days) and within 1 day of a positive SARS-CoV-2 test in 70% of patients. Urine NGAL and KIM-1 assays were blinded to clinical data. Primary outcomes included the diagnosis of Acute Kidney Injury (AKI) as defined by AKIN criteria, as well as its duration and severity. Secondary outcomes included death, dialysis, shock, respiratory failure, and length of hospital stay. Kidney biopsies from COVID-19 patients were examined for biomarker gene expression.

Results: Elevated urinary NGAL (uNGAL) levels were associated with Scr based AKI (267±301 vs. 96±139 ng/mL; P=1.6x10-6). uNGAL level >150 ng/mL had 80% specificity and 75% sensitivity to diagnose AKIN stage 2 AKI or higher. Higher uNGAL levels were associated with sustained AKI [aOR per SD of uNGAL (95%CI): 2.67 (1.81-4.06), P=1.8x10-5], need for dialysis (aOR: 3.67 (1.89-7.57), P=2.2x10-3), shock (aOR: 1.64 (1.26-2.15), P=2.9x10-3), prolonged length of stay (aHR: 1.22 (1.09-1.36), P=4.8x10-5), and death (aOR:1.62 (1.19-2.24), P=2.5x10-3), independent of baseline Scr and pre-existing co-morbidities. These associations were also preserved after adjusting for proteinuria measured in the same urine sample. NGAL is typically transcribed by distal nephron segments but in COVID-19 kidney biopsies with widespread histopathologic acute tubular injury (ATI), NGAL mRNA expression included proximal tubules.

Conclusions: Elevated uNGAL in patients admitted with acute COVID-19 was associated with the development of AKI, increased severity and duration of AKI, the degree of histopathologic acute tubular injury, shock, prolonged hospitalization, need for dialysis, and death.

Funding: NIDDK Support

PO0173
Readmissions After AKI in Colorectal Carcinoma Are Associated with Adverse Outcomes: Findings from the National Readmission Database

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Background: Acute kidney injury (AKI) is common in critically ill cancer patients with poor outcomes. Colorectal carcinomas (CRC) are frequently associated with AKI, due to complications of disease or treatment. AKI in CRC remains a well-known but under-represented topic in current literature. We aim to analyze and quantify the impact, healthcare burden, readmission rates and predictors of metastatic CRC with AKI.

Methods: We conducted a retrospective cohort study of the 2017 National Readmission Database (NRD) of adult patients readmitted within 30 days after an index admission for AKI with a concomitant diagnosis of CRC. ICD 10 codes were used to identify diagnoses and procedures.

Results: A total of 2,239 patients with metastatic colorectal cancer were admitted with AKI. The 30-day readmission rate was 27.9%. Main causes for readmission were sepsis, progression of malignancy, hypovolemia and recurrent AKI. Readmitted patients were associated with higher in-hospital mortality (0.1% vs. 1.5%; p=0.01), mechanical ventilation need (4.7% vs 1.5%; P=0.01) and chronic kidney disease (CKD) diagnosis (44.6% vs 36.1% P=0.01). The total health care in-hospital economic

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
burden of readmission was $32.3 million in total charges and $7.8 million in total costs. After adjusting for age and comorbidities, independent predictors of readmission were disposition against medical advice, HIV, CKD, and sepsis. Preventive factors for readmission were found to be radiation therapy and potentially parenteral nutrition.

Conclusions: AKI in metastatic CRC has a high rate of readmissions, with poor outcomes in morbidity, mortality, and costs making it a significant healthcare burden. Among common causes of readmission, potentially targetable causes include hypovolemia and sepsis while among readmission predictors, CKD and sepsis warrant further attention. Abovementioned preventive predictors consolidate the importance of combination therapy and supportive care in CRC.

Predictors of Readmissions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1.75 (1.68-1.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD</td>
<td>2.04 (1.58-2.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0.45 (0.34-0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.19 (1.08-4.40)</td>
<td>0.025</td>
</tr>
<tr>
<td>Peripheral perfusion defect</td>
<td>0.83 (0.74-0.93)</td>
<td>&lt;0.001</td>
</tr>
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</table>

(a) Derived in the development cohort (b) P < 0.001 for predicting outpatient AKI in the validation cohort.

PO0174 Risk for AKI in the Outpatient Setting

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Background: Risk-factors for acute kidney injury (AKI) in the hospital have been well studied. Yet, tools for identifying outpatients at high risk for AKI are not available.

Methods: A development cohort for modelling risk of AKI without concurrent or subsequent hospitalization was defined by repeated primary care encounters in an urban healthcare system. An external validation cohort was similarly defined in the Veterans Health Administration. Logistic regression with bootstrap sampling for backward stepwise covariate elimination was used to develop a model for outpatient AKI in an 18-month outcome period. The model was then transformed into two binary tests to identify high-risk patients: one for research and another for clinical care.

Results: Outpatient AKI occurred in 4611 of 152,371 (3.0%) and 115,744 of 4,864,576 (2.4%) patients in the development and validation cohorts, respectively. The research test had sensitivity of 0.21 (95% CI: 0.21-0.21) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test, with a lower test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.95 (95% CI: 0.95-0.95).

Conclusions: The outpatient AKI-risk prediction model performed well in both continuous and binary forms.

Performance in the validation cohort of two binary tests for outpatient AKI in 18 months

(a) Derived in the development cohort (b) P < 0.001 for predicting outpatient AKI in the validation cohort.

PO0175 Additive Harmful Effects of AKI and Acute Heart Failure on Mortality in Hospitalized Patients

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Background: Organ crosstalk between kidney and heart has been suggested. This study aimed to investigate the additive effect of both conditions on mortality.

Methods: We retrospectively recruited 102,721 hospitalized patients for 5 years. Acute kidney injury was diagnosed with serum creatinine-based criteria, and acute heart failure with International Classification of Diseases code, within two weeks after admission. Primary outcome was all-cause mortality.

Results: Among the 5,316 (5.2%) patients who died, 20.5% died within 1 month. Hazard ratio for 1-month mortality was 23.25 in patients with both conditions, 13.47 for acute kidney injury only, and 2.76 for acute heart failure only. The relative excess risk of interaction was 8.01, and it was more prominent in patients aged <75 years, and those without chronic heart failure.

Conclusions: Acute kidney injury and acute heart failure had a detrimental additive effect on short-term mortality in hospitalized patients.

Results of analyses on interaction, where AKI and AHF are the two exposures of interest to mortality within 1 month

Relative excess risk of interaction (95% CI) = 1.453 (2.386-20.520); P = 0.013. Attributable proportion due to interaction (95% CI) = 0.401 (0.208-0.594); P < 0.001. Synergy index (95% CI) = 1.710 (1.224-2.388); P = 0.002. AKI, acute kidney injury; AHF, acute heart failure; HR, hazard ratio; CI, confidence interval.

Kaplan-Meier curves for death by groups, based on presence of AKI or AHF
AKI: Epidemiology, Risk Factors, and Prevention

Poster

PO0176
Clinical Trajectories of AKI and Clinical Outcomes in Acute Decompensated Heart Failure
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Background: Cardiorenal syndrome (CRS) is a pathophysiologic disorder of the heart and kidneys, with both acute and chronic dysfunction. Type 1 CRS is characterized by an acute cardiac disease leading to AKI.

Methods: This is a retrospective cohort study from Jan 2017 to Dec 2018 in 3rd level center in Mexico City. The objective was to describe the incidence and outcome of AKI in patients with CRS type 1. We divide AKI’s trajectory into: ascending and descending AKI, also we used a creatinine (Cr) cut-off point of 1.5 mg/dl and identified 6 trajectories. We used a Logistic regression analysis (LRA) for in-hospital mortality and length of stay.

Results: 404 patients were included. Mean age 58.9 ± 16.6 years, 60% were men, 27% had DM, 45% had hypertension. The incidence of AKI was 60.9% and mortality was 22%. Severe AKI in 25.5%, 36 (8.9%) required kidney replacement therapy. The incidence of ascending AKI was 29.7% and mortality in this group was 46.7%. AKI’s trajectory are shown in Figure 1. In LRA for the whole cohort, PASP ≥40 mmHg (OR 4.82 CI 2.01-11.6 p<0.001), NT-proBNP >10000 (OR 3.26 CI 1.61-6.57 p=0.001), ascending AKI (OR 4.08 CI 2.11-7.88 p=0.04) were associated with mortality. In LRA for ascending AKI, BUN/Cr ratio >25 (OR 1.9 CI 1.00-2.54 p=0.001) and neutrophil/lymphocyte ratio (NLR) >6.5 (OR 2.64 CI 1.65-4.23 p=0.001) were associated with in-hospital mortality.

Conclusions: The incidence and mortality of AKI in patients with decompensated heart failure is high. Patients with ascending AKI had a significant increase in mortality and descending AKI had a better prognosis. Different Cr trajectories indicate different outcomes, the group of patients who at the time of admission had Cr >1.5mg/dl and presented a rise during hospitalization had a worse outcome. NLR>6.5 and BUN/Cr ratio >25 are predictors of mortality.

PO0177
National Epidemiology of Community-Acquired AKI
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Background: Community-acquired acute kidney injury (CA-AKI) is AKI that develops outside of the hospital and is the most common form of AKI globally. National estimates of CA-AKI in the US are absent due to lack of integrated health data and limited availability of outpatient lab data. In this study, we leverage data from the Veterans Health Administration (VA) to estimate CA-AKI incidence and risk factors.

Methods: We constructed a retrospective cohort using national VA administrative and lab data to assess the cumulative CA-AKI incidence among active VA primary care users in 2013-2017. Veterans who did not have recorded outpatient serum creatinine (Scr) and those with a history of severe kidney disease (a Scr ≥2.0 in the previous 24 months) were excluded. CA-AKI was defined as a creatinine increase of ≥0.3 mg/dL from baseline. The primary outcome was subsequent hospitalization for congestive heart failure (CHF), myocardial infarction (MI), or stroke (MACE), with follow-up of at least 2 years. Over 50 variables were considered for inclusion in the final model. Bootstrap modeling was used to determine the outcomes of 100 stepwise regressions using random sampling with replacement. Variables included in more than 60 were included in a final model using Cox proportional hazards models. If not selected, AKI stage was forced into the model. Due to the association between cardiac disease and the primary outcome, and in order to evaluate risk factors for de novo cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease.

Results: A total of 241,781 Veterans with AKI were included. AKI stage did not meet selection criteria for either model. In patients without pre-existing cardiac disease, the final model included age, sodium, bilirubin, chronic lung disease (COPD), complicated diabetes mellitus (CXM), atrial fibrillation (A-Fib), and proteinuria. AKI stage 3 (HR 1.10, 95% CI 1.08-1.1) compared to AKI stage 1 was a weak predictor of subsequent MACE events. Similarly, in patients with prior cardiac disease, the final model included age, blood urea nitrogen, white blood count, CHF, MI, COPD, CxM, A-Fib, cardiomyopathy, cardiac device, sleep apnea, complicated hypertension, valvular disease, major electrolyte abnormalities, and proteinuria. AKI stage 3 was again a weak predictor (HR 1.065, 1.03-1.1).

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Underline represents presenting author.
Conclusions: While AKI stage is commonly used to enroll patients into AKI survivorship clinics, it was not found to be a strong independent predictor of MACE events among post-AKI Veterans. Our findings may inform risk stratification for post-AKI follow up.

PO0180
Urinary Oxygen Partial Pressure to Monitor AKI Risk
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Background: In a prior study, we showed that patients who developed acute kidney injury (AKI) had lower mean urinary oxygen partial pressure (PuO2) following cardiopulmonary bypass (CPB). However, PuO2 is unreliable when urine flow is low and little is known about the distribution of urine flow intraoperatively. The objective of this research was to determine the distribution of the length of sections of unreliable PuO2 data due to low flow.

Methods: Following IRB approval and informed consent, a device that measures PuO2 and urine flow was placed in cardiothoracic surgery patients. PuO2 and urine flow (sampled at 1 Hz) were deemed reliable when the flow was above a threshold. Patients who did not meet a percent valid data threshold were excluded. Mean PuO2 following CPB and the maximum and median length of sections of invalid data were calculated. Data were generated for a percent valid data threshold of 30% and urine flow rate thresholds of 0.1 to 1 mL/kg/hr at 0.1 increments. Patients who met the KDIGO criteria for AKI were compared to non-AKI patients. In addition, patients with Stage 2 or 3 AKI based on the KDIGO serum creatinine criteria were assigned to the Severe AKI group and were compared to patients with stage 1 or no AKI. The area under the curve (AUC) of a receiver-operator (ROC) plot of mean PuO2 estimating AKI development was calculated for each comparison.

Results: AUC was 0.69 for AKI when the flow threshold was 0.4 ml/kg/hr. The average for all patients of the median and maximum length of invalid data was 37 seconds and 387 seconds, respectively. For Severe AKI, the AUC was 0.81 for a flow threshold of 0.7 ml/kg/hr. As the maximum length of invalid data sections increases the AUC decreases.

Conclusions: Sections of unreliable PuO2 data are sufficiently short and do not significantly impact the performance of PuO2, as a marker of AKI when a urine flow threshold is used to filter the data. The data demonstrate the feasibility of measuring PuO2 to monitor AKI risk during cardiothoracic surgery. Further research is needed to determine if intraoperative PuO2 can reduce the incidence of AKI.

AUC of mean PuO2 and distribution of length of invalid data sections

PO0181
Serum Trace Metal Changes Could Potentially Indicate Kidney Damage in Rats with Cisplatin-Induced Kidney Injury
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Background: Cisplatin (CDP), a widely used anticancer drug, is known to exhibit nephrotoxicity in adverse effects. Nephrotoxicity is a dose-limiting toxicity. Therefore, the early detection of cisplatin-induced nephrotoxicity is crucial. Certain trace metals reportedly change with kidney injury, although their relationship with CDP-induced kidney injury remains unclear. Therefore, in this study, we investigated the trace metal changes after cisplatin treatment in rats.

Methods: Eight-week-old male Wistar-ST rats were divided into a control and a CDP group (n = 6 for both), treated intraperitoneally with saline or CDP for 3 mg/kg, respectively. On day 0 and 5, we took serum samples and measured the SCr and BUN levels. The kidneys were obtained on day 5 and subjected to histological studies using HE staining. The serum samples were used for the comprehensive measurement of nine different trace metal types (Mn, Fe, Co, Ni, Cu, Zn, As, Se, and Mo) by ICP-MS. The statistical analysis was performed using Student’s t-test.

Results: The SCr and BUN levels significantly increased in the CDP group compared with those in the control group (P<0.01). The HE staining showed that the proximal tubular injury in the CDP group was severe compared to that in the control group. Three out of nine serum trace metals, Co, Ni, and Cu, were significantly high in the CDP group compared with those in the control group (P<0.01).

Conclusions: Co, Ni, and Cu increased after the CDP treatment. The measurement of such elements could be useful for the detection of CDP-induced nephropathy.
Venkatasubramanian, Therapy: Correlation of Mean Platelet Volume with Mortality at AKI: Epidemiology, Risk Factors, and Prevention

PO0184

Recovery After AKI: Goals of an AKI!Now Workgroup
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Background: The American Society of Nephrology recently established the AKI!Now initiative. AKI!Now aims to promote excellence in the prevention and treatment of AKI by transforming the delivery of AKI care to improve clinical and patient-centered outcomes. Herein, we describe the focused efforts of AKI!Now on “recovery after AKI.”

Methods: Three core objectives were identified in the domain of AKI recovery: 1. To determine areas of priority for mechanistic research focused on recovery after AKI. It is expected that these would include a variety of experimental models suitable for various AKI etiologies and disease severities. 2. To benchmark patient care to better understand care for patients after AKI including integrated insights from primary care providers, nephrologists, other subspecialty health care professionals. 3. To facilitate implementation and testing of interventions designed to limit short- and long-term complications of AKI and promote recovery. Analysis dependent and independent AKI survivors should both be considered for these interventions and clinical trials.

Results: The AKI!Now initiative will highlight and clarify challenges and opportunities to improve care after AKI. This work will also inform who is followed after AKI and by whom (i.e., primary care and/or nephrology), options for care delivery (i.e., in-person versus telehealth), and potential practices to improve outcomes (i.e., role of ACEi/ARB and SGLT2 inhibitors after AKI, physical/cognitive rehabilitation). The stakeholder relationships formed, including those with patients, healthcare professionals, industry, and academia, will facilitate a collaborative research and practice agenda necessary to understand and outline best practices after AKI.

Conclusions: Survivors of AKI are a high-risk and growing population, and AKI is associated with worse long-term outcomes than an acute myocardial infarction. However, how to care for patients after AKI remains ill-defined with substantial practice variation. This represents an opportunity for the “recovery after AKI” workgroup of AKI!Now to provide leadership by raising awareness and promoting strategies focused on equitable and effective post-AKI care throughout the American Society of Nephrology and wider nephrology community.

PO0185

Exploration of the Mitochondria Genes Alteration in AKI
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Background: Acute kidney injury (AKI) is one of the most common complications in clinic, especially in critical ill patients. Recently, the fundamental function of mitochondria in acute kidney injury and repair have gradually been noticed while the mechanism still unclear. Therefore, we aimed to identify the change pattern of mitochondria alteration associated gene in AKI through Gene Expression Omnibus (GEO) database analysis and AKI animal model verification.

Methods: A total of 1893 genes involved in mitochondria function and metabolism were screened from Gene Ontology (GO) database and defined as GO terms in mitochondria metabolism. Meanwhile, 2 studies invests transcriptome differences in renal ischemia reperfusion injury (GSE98622 and GSE99703) were extracted from GEO database. By crossing GO terms and 2 datasets from GEO database, 69 and 62 mitochondria metabolism genes were identified in GSE98622 and GSE99703 separately. Among which, 23 genes were overlapped in 2 datasets and verified by real-time PCR in 2 kinds of AKI model (ischemic renal reperfusion injury model and cisplatin induced AKI model).

Results: Through GO and KEGG enrichment analysis, these differentially expressed genes (DEGs) were allocated to peroxisome, butanoate metabolism, arginine and proline metabolism, neurotrophin signaling pathway and metabolic pathways. Protein–protein interaction analysis demonstrated that Hac2, Acsm3, Amacr, Aadat may play vital roles of mitochondrial regulation in AKI. The results of real-time PCR show that 3 genes were significantly increased in both two kinds of AKI model (Arg2, Cli, Lgals3) and 12 genes were decreased (Aadat, Acsm3, Aggs, Akk4, Amacr, Bdn1, Gatm, Has2, Iso2b, Mbp, Vip17, Nat8f1, Ndufb1), while others were not altered in animal model or had no consistency changes between 2 kinds of AKI model.

Conclusions: We have identified 23 DEGs were associated with mitochondria metabolism in I/R AKI by using bioinformatic technology. Among these genes, GO and KEGG analysis suggests that the DEGs are mainly enriched in lipid metabolism, amino
acid metabolism pathway and tightly associated with peroxisome. Furthermore, 15 DEGs were revalidated in kidney of two kinds of AKI mouse model (IR & Cisplatin- AKI).

**Funding:** Government Support - Non-U.S.

**PO0187**

**Artificial Intelligence in AKI: Goals of an AKI!Now Workgroup**

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**Background:** In 2019, the American Society of Nephrology established AKI!Now, a collaborative initiative to promote excellence in the prevention, diagnosis, and treatment of Acute Kidney Injury (AKI). Here, we describe the ongoing efforts of the AKI!Now workgroup focused on Artificial Intelligence (AI) to improve the quality, accessibility, affordability, and equity of AKI care.

**Methods:** The workgroup has outlined objectives in 3 key domains: 1. Patients: Input in designing and implementing fair and equitable AI tools and identifying clinical scenarios based on personal and caregiver experience that could be improved; 2. Clinicians: Input in the design, value, and implementation of fair and equitable AI tools and identifying clinical uncertainties that may benefit from new AI tools; 3. Researchers: Evaluation of current AI tools, with a focus on removing implicit bias; development of novel, feasible, and effective AI tools to address gaps identified by patients and clinicians; and development and implementation of AI methods along with novel sensors for more sensitive assessment of kidney function and injury to advance the science of AKI.

**Results:** This project, with involvement from a multi-disciplinary group of stakeholders, will yield efficient and effective use of AI for quality improvement in AKI care. Specific deliverables include 1) Risk-stratification and prediction tools; 2) Intelligent alert tools; 3) Decision support for bundled care compliance; 4) Decision support for implementing pragmatic clinical trials, among others. Importantly, this work will fill gaps in available AI tools and develop many desired AI tools that do not exist. These coordinated efforts are expected to deliver highly useful AI tools that could improve AKI care, research and reduce associated costs.

**Conclusions:** The AKI!Now workgroup on AI is committed to improving value care in AKI and encourages engagement and collaboration with patient, provider, researcher, and industry stakeholders. We seek to improve the care provided to the growing and susceptible AKI population, along the entire lifespan.

**PO0188**

**Incidence of AKI in Individuals Treated with Lithium**

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**Background:** Lithium has been linked to acute kidney injury (AKI) at toxic blood levels but the risk of AKI has otherwise not been well studied. Interestingly, lithium has been shown to protect against tubular injury in experimental AKI models. The aim of the study was to examine the risk of AKI in individuals treated with lithium.

**Methods:** This was a retrospective cohort study of all individuals treated with lithium in Iceland in 2003–2018. A control group comprised patients with affective disorders (ICD 10 codes F30-F39) attending the outpatient clinic of the Mental Health Services at Landspitali—the National University Hospital in 2014–2016, who had never used lithium. Clinical and laboratory data, including ICD-9 and ICD-10 codes and serum creatinine (SCr) values, were obtained from nationwide electronic medical records. Individuals with <2 SCr values available were excluded. AKI was defined using the SCr component of the KDIGO criteria. Multivariable logistic regression was used for the analysis.

**Results:** The lithium-treated group consisted of 2682 individuals, of whom 2310 (86.1%) were included in the study. Of those, 297 (12.9%) developed AKI. Of 1242 individuals in the control group, 1218 (85.5%) were included and 97 (8.0%) developed AKI. Lithium use was not an independent risk factor for AKI (OR 0.93, 95% CI, 0.72–1.20, Table). When lithium users were analyzed separately, lithium intoxication (OR 2.34, 95% CI, 1.33–4.09), duration of lithium therapy (OR 1.01, 95% CI 1.00–1.01) and mean lithium concentration (OR 1.22, CI, 1.14–1.30) were all significant risk factors for development of AKI.

**Conclusions:** Our findings suggest that lithium use does not affect the incidence of AKI, after controlling for important covariates. However, lithium intoxication, time on lithium therapy and blood lithium concentration are associated with increased risk of AKI.

**Funding:** Government Support - Non-U.S.

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**Factors associated with AKI: multivariable logistic regression.**

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<thead>
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<th></th>
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<tr>
<td>Diabetes</td>
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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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**PO0189**

**Healthcare Analytics with Time-Invariant and Time-Variant Feature Importance to Predict Hospital-Acquired AKI**

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**Background:** Acute kidney injury (AKI) develops in 4% of inpatients and is a marker of clinical deterioration and nephrotoxicity. AKI onset is highly variable in hospital which makes it difficult to time biomarker assessment in patients for preemptive care. We applied machine learning to electronic health records and predict hospital-acquired AKI by a 48-hour lead time, with aim to create an AKI surveillance algorithm that is deployable in real-time.

**Methods:** The data was sourced from 20,732 case-admissions in 16,285 patients over one year in our institution. We enhanced our bidirectional recurrent neural network with a novel time-invariant and time-variant module to capture clinical features temporal to AKI in cases. Time-series features included laboratory parameters that preceded a 48-hour prediction window before AKI onset; the latter’s corresponding reference was the final in-hospital serum creatinine performed in cases without AKI.

**Results:** The cohort was of mean age 53(±25) years, of whom 29%, 12%, 12%, and 53% had diabetes mellitus, ischemic heart disease, cancers, and baseline eGFR <90 mL/min/1.73m², respectively. There were 911 AKI episodes in 869 patients. We derived and validated an algorithm in the testing dataset with an AUROC of 0.81 (0.78-0.85) for predicting AKI. At a 15% prediction threshold, our model generated 699 AKI alerts with 2 false positives for every true AKI and predicted 26% of AKIs. A lowered 5% prediction threshold improved the recall to 66% but generated 3,746 AKI alerts with 6 false positives for every true AKI.

**Conclusions:** We generated an accurate algorithm from electronic health records through machine learning that predicted AKI by 48 hours prior. The prediction threshold could be adjusted during deployment to balance an optimal recall with alert-fatigue, while its precision could be augmented by better-timed AKI biomarker assessment in the high-risk cohort identified.

**Funding:** Government Support - Non-U.S.

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**Underline represents presenting author.**
Urine Biomarkers of AKI in Extremely Low Gestational Age Neonates: A Case-Control Study

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Background: Urine biomarkers hold promise to diagnose and differentiate AKI. In premature neonates, biomarker evaluation must address normative gestational age (GA) differences.

Methods: We performed a case-control study from neonates enrolled in the Preterm Erythropoietin Neuroprotection Trial (PENUT) to evaluate differences in urine obtained in the first postnatal week between cases and controls. Twenty (N=20) neonates with severe AKI (Stage 2 or 3) were matched with 2 controls (N = 40) who did not have AKI, had the same GA week (rounded down to the nearest week), gender, and BW (±/− 50 g), without replacement. Biomarkers were analyzed on multi-analyte electro-chemiluminescent or single colorimetric ELISA kits. Biomarker were run in duplicates; the average concentration was converted to log10. Days were grouped into day 0-3, 4-6, 7-9, with day of birth was defined as day 0. For each biomarker, the average pairwise difference between cases and controls was calculated. To account for multiple measurements, a linear mixed model framework was employed incorporating a random intercept for match, random effects across day, and a day case status interaction term. The predicted mean differences (95% CI) between cases and controls for each measurement time frame are compared and reported in the figures.

Results: Demographic characteristics were similar between those with and without AKI. The association with case status was modified by day (interaction p-values <0.05) for (Albumin, Clusterin, Creatinine, Cystatin C, epithelial growth factor (EGF), kidney injury marker-1 (KIM1), neutrophil gelatinase associated lipocalin (NGAL), FGF23, Glicelin, IGF8P7, IL-15, MCP1, TIMP2, VEGFA). Figures show a forest plot of the predicted mean differences (case minus control) at days 1 (0-3), 5 (4-6), and 9 (7-9) for each of 21 urine biomarkers. Urine albumin (day 1), EGF (day 1), creatinine (day 5 and 9), Cystatin C (Day 9), KIM-1 (day 9), IL-15 (day 9), and VEGFA (day 5) were significant differences between cases and controls.

Conclusions: Several urine biomarker concentrations differed in extremely low gestational age neonates with severe AKI vs. control. Further evaluation of these biomarkers is required before clinical utility can be addressed.

Funding: Other NIH Support - Recombinant Erythropoietin for Protection of Infant Renal Disease (REPaReD) Study is an NIH NIDDK funded (R01 DK103608) ancillary study designed to look at kidney outcome in patients enrolled in the Preterm Erythropoietin Neuroprotection Trial (PENUT) which is an NIH NINDS funded (U01 NS077953, U01 NS77955) trial. The clinicaltrials.gov identifier is NCT01378273.

Predictors and Outcomes of Post-Left Ventricular Assist Device AKI

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Background: Left ventricular assist device (LVAD) is used to treat advanced heart failure as a bridge to orthotopic heart transplant (OHT) or as destination therapy in patients who are not OHT candidates. With limited donor availability and significant improvement in LVAD outcomes, the number of patients with LVAD implantation as destination therapy has increased. With increased LVAD use, the number of adverse events and complications are expected to increase. Acute kidney injury (AKI) is a frequent complication after LVAD implantation and is associated with high mortality. We studied the predictors of Post-LVAD AKI and the association between AKI and mortality, as well as between AKI and receiving an OHT.

Methods: We conducted a retrospective multi-center study using TriNetX Research Network database, a federated electronic medical records, to identify 486 patients from 24 healthcare organizations from the United States, with no underlying chronic kidney disease (CKD) who had an LVAD implanted between 1/1/2010 and 12/31/2019. Of these, 116 (24%) had developed AKI within the first month of the procedure. The baseline characteristics of this group were compared with the 370 patients who had not developed AKI during the first month after LVAD placement.

Results: There was no statistically significant difference between the two groups in regards to age at time of LVAD placement, sex, or ethnicity. Black race was associated with a higher odds of developing AKI (Odds Ratio [OR]: 1.70; 95% Confidence Interval [CI]: 1.11, 2.59). The two co-morbidities most significantly associated with AKI during the first month after LVAD placement were: persistent atrial fibrillation (OR: 3.33; CI: 1.25, 8.22), and a body mass index (BMI) > 50 (OR: 3.86; CI: 2.21, 6.75). During the first year after LVAD placement, 73 patients died and 37 patients received OHT. There was no statistical difference in one-year mortality or likelihood of undergoing an OHT within a year between the AKI and non-AKI groups.

Conclusions: In patients with no underlying CKD, black race, persistent atrial fibrillation, and BMI above 50 increase the likelihood of post-LVAD AKI. Development of AKI post-LVAD implantation in these patients is not associated with changes in one-year mortality or likelihood of receiving an OHT.

Associations of RAS Inhibitor Suspension During AKI with Mortality in Hospitalized Patients

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Background: Blockade of the renin-angiotensin system may slow disease progression and prevent mortality in patients with chronic kidney disease. However, it is unclear whether RASI can increase the risk of developing AKI and its complications in hospitalized patients. The aim of the study is to compare mortality of patients with AKI who have discontinued RASI to those who maintained its use.

Methods: We analyzed data from a cohort of hospitalized patients identified by an AKI alert based on KDIGO creatinine criteria, who were on a RASI. From January to December 2018, suspension of RASI medications was defined by the medication was suspended until 3 days after AKI alert in their electronic health records. Cox models were used to test the association of RASI suspension with all-cause mortality, adjusting for possible confounders: age, sex, race, baseline and worst achieved GFRs, potassium, hemoglobin levels and episodes of hypotension during the hospitalization.

Results: During hospitalization 1253 patients were on a RASI. After the AKI alert, 493 remained and 760 suspended its use. The median [IQR] follow-up time was 11.9 [7.20-20.8] days. Patient characteristics were similar across treatment strategies. In the RASI group, AKI mortality rates were 33% vs 25%, which were significantly different (p=0.03). There was a trend towards higher AKI mortality in patients who discontinued RASI compared to those who maintained its use (38% vs 25%, p=0.05).
AKI: Epidemiology, Risk Factors, and Prevention

PO0194
External Validation of Simple Postoperative AKI Risk (SPARK) Classification in Noncardiac Surgery: The NARA-AKI Cohort Study
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Background: The aim of the present study was to externally validate Simple Postoperative AKI Risk (SPARK) index which was developed to predict post-operative acute kidney injury (PO-AKI) in non-cardiac surgery.

Methods: In a retrospective cohort study, adults with non-cardiac surgery under general anesthesia were included. Those with obstetric or urological surgery, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m², pre-operative dialysis, expected surgical duration <1 hour, and missing data for analyses were excluded. The exposures of interest were risk factors for AKI included in SPARK index, and outcomes were PO-AKI and critical AKI. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively.

Results: Among 5135 subjects, 303 and 137 developed PO-AKI and critical AKI, respectively. Subjects in our cohort were older, and baseline eGFR was lower compared to SPARK cohort. In addition, the proportion of subjects with comorbidities was higher. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively.

Conclusions: The aim of the present study was to externally validate Simple Postoperative AKI Risk (SPARK) index which was developed to predict post-operative acute kidney injury (PO-AKI) in non-cardiac surgery.

PO0195
A Risk Score for Major Adverse Kidney Events One Year After AKI
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Background: Epidemiologic evidence suggests that those with AKI are at increased risk of post-AKI kidney disease, higher hospital resource utilization, and death. However, literature to support identification of those most at risk of these outcomes is limited. Here we pilot predicting risk of post-AKI MAKE.

Methods: In a cohort of 4.2 million United States Veterans, risks of MAKE within a year of discharge associated with an AKI were detailed using survival regression with inverse probability of treatment weighting. Risk factors for MAKE including demographics, clinical characteristics including diagnoses, medication use, and laboratory tests, as well as hospitalization parameters among those with an AKI were examined, and then a risk score was developed and evaluated following the Framingham Heart risk score algorithm.

Results: In the year after discharge form a hospitalization, compared to those without an AKI, those with an AKI were at an increased risk of a subsequent AKI (HR=1.47; 95% CI=1.45-1.49), incident eGFR less than 60 mL/min/1.73 m² (1.23; 1.22-1.24), eGFR decline >30% (1.69; 1.67-1.71), receipt of kidney replacement therapy (2.41; 2.28-2.51), and MAKE (1.24; 1.23-1.25). Results were consistent in Fine and Gray competing risk models. Among those with an AKI, predictors of MAKE included age, albuminuria, bicarbonate, blood pressure before and during hospitalization, cardiovascular disease, cancer, chronic lung disease, dementia, diuretic use, baseline eGFR, hematocrit level, NSAID use, obesity, platelet count, pneumonia, serum creatinine trajectory during hospitalization, surgeries, and urinary tract infection. A risk score constructed using these predictors achieved an area under the curve (AUC) of 0.72, where corresponding probabilities of having a MAKE within a year of discharge ranged from 7.5% to 59.9% at the lowest and highest risk score values experienced in the cohort. Comparatively, use of KDIGO stage alone marginally predicted future risk of MAKE (0.52). Calibration plots suggested that models were well calibrated.

Conclusions: Use of EHR resulted in a moderate ability to identify those at increased risk of post-AKI MAKE. Further research is needed in identifying those who may benefit from post-AKI care.

Funding: Veterans Affairs Support, Private Foundation Support
PO0197
Chikungunya Fever: A Trigger for Different Renal Disorders
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Background: Prevalence of chikungunya fever (CHIK)–related kidney injury (KI) is variable, but data are scarce and limited to the acute phase of the disease. Necropsies performed in fatal acute cases of CHIK virus RNA can be found in renal tissue, but clinical and histopathological aspects poorly characterized. This study aimed to describe renal histopathological features and to detect viral antigens in renal tissue in patients affected by CHIK in different phases of infection.

Methods: This was an exploratory study, conducted between 2016 and 2020. Patients followed in six nephrology reference centers due to KI with onset after different phases of CHIK infection were evaluated. These patients had hematoma, proteinuria and/or renal dysfunction. They were reviewed with regard to medical history. Logistic regression was used to identify factors associating with AKI.

Results: Sixteen patients (aged 10-59 years) had KI 0.5 to 24 months after CHIK, with predominance of glomerular lesions. Initial creatinine ranged from 0.2 to 22.3 mg/dl (median 3.9 mg/dl, IQR 1.0-5.5). Proteinuria and hematoma were initially detected in 94% and 81% of patients, respectively. Histopathological findings comprised diagnoses of focal segmental glomerulosclerosis (FSGS) (3), class IV lupus nephritis (3), crescentic glomerulonephritis (2), atypical hemolytic uremic syndrome (aHUS) (2), paraproteineemia vasculitis (1), PLA2R-positive membranous nephropathy (2), collapsing glomerulocapsum (CG) (2). One patient was diagnosed with collagen IV-related nephropathy in renal biopsy performed due to macroscopic hematuria after CHIKV infection. No viral antigens were detected in renal tissue. Two patients with aHUS included in the study carry heterozygous mutations associated with increased risk of developing the disease. APOLI high-risk genotypes were identified in 2 patients with CG (G1/G2 and G2/G2) and 1 patient with FSGS (G1/G2). Nine (56%) patients progressed to chronic kidney disease after a median follow-up of 12 months.

Conclusions: Our data reveal the potential of CHIK virus to directly cause and/or trigger KI. These effects can be translated into a variety of renal lesions potentially with significant severity.

PO0198
Risk Factors and Outcome Variables of Cardiorenal Syndrome Type 1 from the Nephrological Perspective
Daniel Patsch, Medical School of Brandenburg, Brandenburg, Germany.

Background: In cardiorenal syndrome (CRS) type 1, acute cardiac failure or acute decancellation of chronic heart failure causes acute kidney injury (AKI). Every individual AKI episode increases the risk for chronic kidney disease (CKD) in the long-term. In this study we aimed to evaluate epidemiological characteristics and outcome variables of CRS type 1 individuals from the nephrological perspective.

Methods: The study was performed in a retrospective, observational manner. All AKI patients treated at the Brandenburg Hospital of the Medical School of Brandenburg between January 1, 2019 and June 30, 2019 were screened. Diagnostic criteria of CRS type 1 endpoints were in-hospital death, need for dialysis, and renal recovery.

Results: During the screening, a total number of 1,189 subjects were diagnosed with acute kidney injury according to KDIGO. One-hundred ninety-eight (198 - 16.6%) out of these patients were assigned to the diagnosis CRS type 1. The overall in-hospital mortality was 19.2%. Non-survivors were not older than survivors. Nine point six (9.6) % of the patients required dialysis due to AKI, respective individuals were significantly older (84.6 +/-1.14 vs. 77.6 +/-0.7 years; p=0.002). Complete recovery of kidney function was observed in 86% of patients (43.4%), incomplete recovery occurred in 55 patients (27.8%), fifty-seven patients (28.8%) did not recover at all. Age-related differences were not identified. Sixty-four (32.2%) demission letters did not contain any cardiovascular diagnosis at all, nephrology follow-up recommendations were given in only 8%.

Conclusions: The incidence of CRS type 1 is high (~16% of all in-hospital AKI subjects) and the mortality is higher than the average mortality of AKI in general. At the same time complete recovery of kidney function occurs less frequent. The kidney-related follow-up management of CRS type 1 needs to be significantly optimized in order to improve the long-term outcome of affected patients.

PO0199
An Automated, Open-Source Program to Standardize AKI Definition from Time-Stamped Creatinine Data
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Background: Though KDIGO guidelines specify a definition for AKI based on changes in serum creatinine, operationalizing this definition with real-world data requires multiple assumptions that leads to variation across studies. A standardized AKI flagging tool that improve inter-study validity.

Methods: We developed AKIFlagger, an open-source computational tool built in Python, R, and as a web application which implements a standardized AKI definition based on KDIGO guidelines while allowing for variational definitions of baseline creatinine. We applied the AKIFlagger to a dataset of patients hospitalized with COVID-19 while permitting various operational implementations of the guidelines.

Results: We demonstrate that subtle changes in definition can have a large impact on estimates of AKI prevalence and outcomes. Compared to a rolling window approach, using a baseline definition that leverages outpatient creatinine values and or imposes those values based on an eGFR back-calculation increases the size of captured patient populations by 20.7% and 57.1%, respectively. We characterize the predictive value of the different methods of identifying AKI by determining the sensitivity and specificity for stage progression and progression to death or dialysis. The approaches span sensitivities from 0.18 to 0.20 and specificities from 0.90 to 0.95 for stage progression, and sensitivities from 0.71 to 0.85 and specificities from 0.62 to 0.76 for progression to death.

Conclusions: Subtle differences in the definition of AKI can lead to drastic differences in which patient populations are captured by the definition. A standard method to implement the KDIGO criteria is necessary for the field to accurately advance both clinical and basic science research. This standardized tool can be used by researchers to ensure definitions are uniform across studies.

Funding: NIDDK Support

Screen shot of the web interface for AKIFlagger

PO0200
Community-Acquired AKI: A Prospective Case-Control Study
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Background: Acute kidney injury (AKI) represents an abrupt decline in kidney function occurring over hours or days. While hospital-acquired AKI has been extensively studied, data on community-acquired AKI are scarce. The aim of this study was to examine the incidence and causes of AKI among patients presenting to the emergency department (ED).

Methods: This was a prospective case-control study in which serum creatinine (Scr) of all individuals admitted to the ED of Landspitali–The National University Hospital were examined for the presence of AKI. We present data from January 1 until March 3, 2020 and May 1 until September 2, 2020. The study was paused between these periods due to the COVID-19 epidemic. All patients who met the KDIGO criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex and time of ED admission. Participants answered questions about their medical history and use of medications, including over-the-counter (OTC) drugs. Medical records were reviewed with regard to medical history. Logistic regression was used to identify factors associating with AKI.

Results: A total of 372 persons with AKI were identified, 315 (85%) of whom participated in the study. The mean (±SD) age of AKI cases and controls was 66.4±1.1 years and 66.3±1.6 years, respectively; 46% of cases and controls were female. AKI cases were significantly more likely than controls to have used non-steroidal anti-inflammatory drugs (NSAIDs) (31.1% vs 22.2%, p=0.003) in the week preceding the ED visit, particularly the NSAIDs (24.7% vs 16.2%, p=0.001). In a multivariate logistic regression analysis, AKI was associated with vomiting (OR 2.40 95%CI 1.74-3.35), diarrheea

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(OR 1.35, 95%CI 1.00-1.84), diabetes (OR 1.66, 95%CI 1.17-2.35) and NSAID use (OR 1.60, 95%CI 1.18-2.23), but a statistically significant relationship was not observed for use of ACE inhibitors/angiotensin receptor blockers or diuretics, or a history of hypertension, vascular disease or chronic kidney disease.

**Conclusions:** These results suggest that volume depletion and the use of NSAIDs play a major role in the development of AKI in the community setting. Frequent use of OTC NSAIDs is a concern and should be addressed in light of serious adverse effects.

**Funding:** Government Support - Non-U.S.

### PO0203

**Circulating Endotoxin Levels Correlate with Kidney and Mortality Outcomes in Critically Ill Patients**

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**Background:** Among the critically ill, sepsis is a common cause of acute kidney injury (AKI). Endotoxin is a component of gram negative bacterial cell walls, and is a potent trigger of AKI in sepsis, but may also be present in non-bacteremic patients. Our aim was to determine correlations between endotoxin levels and AKI and mortality outcomes in incident critically ill patients.

**Methods:** Patients were recruited from those admitted to intensive care units (ICUs) who were over 18, and who did not have end-stage renal failure requiring dialysis, or were receiving immunosuppressive medications. Blood endotoxin activity (EA) was measured using the FDA-approvenchemiluminescent EA Assay. Blood EA was measured on days 1, 4, and 8 of admission to ICU, and results either categorized as low (0.0-0.39), intermediate (0.4-0.59) or high (≥0.60), or used as a continuous variable in Spearman correlation analysis. Kidney parameters and dispositions were obtained from electronic medical records. AKI was defined as per KDIGO guidelines.

**Results:** A total of 35 patients were recruited between November 2020 and April 2021, with 4 testing positive for gram negative bacteria. Initial EA levels were 6 (17%), 10 (29%) and 19 (54%) patients with low, intermediate, and high levels, respectively. During the study, 14 patients’ EA levels changed such that their categorization either went up (4) or down (9), whilst one patient alternated between intermediate and high levels. When stratified by presence of AKI, no patients with low EA (0/6) developed AKI, whilst 9/13 (71%) of patients with AKI had high EA versus 8/20 (40%) of non-AKI patients who had high EA. All of the patients with low EA were discharged, whereas 3/10 (30%) and 4/18 (22%), respectively, of those with intermediate and high EA expired. When analyzed as a continuous variable, there was a significant positive correlation between initial EA and subsequent mortality. Furthermore, there was a significant correlation between the rates of changes in EA and sCr over time (r = 0.47, p<0.05).

**Conclusions:** Endotoxin levels on admission to ICU correlated with kidney function, presence of AKI, and mortality. Changes in EA over time also correlated with changes in kidney function, suggesting that EA may be a potential biomarker in critically ill patients.

**Funding:** Commercial Support - Dialysis Clinic Inc

### PO0204

**Incidence of Hypophosphatemia During Continuous Renal Replacement Therapy: Baseline Data for a Quality Improvement Initiative**

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**Background:** Hypophosphatemia is common among critically ill patients on continuous replacement therapy (CRRT). And low serum phosphorus is associated with difficulty to wean off from mechanical ventilation, longer hospital stays, and death. Our objective was to determine the incidence of hypophosphatemia among individuals receiving CRRT before implementing a phosphate replacement protocol as part of a quality improvement initiative.

**Methods:** We conducted a retrospective study of electronic health records from the University of Arkansas for Medical Sciences to identify consecutive adults diagnosed with acute kidney injury who received CRRT for at least 24 hours between May 2014 and September 2018. Laboratory measurements of serum phosphorus collected while on CRRT were examined for hypophosphatemia as defined as levels <2.5 mg/dL.

**Results:** A total of 685 unique patients received CRRT between 2014 and 2018. On average, 13.2 individuals were started on CRRT every month. Of 685 individuals, 446 were on CRRT for at least 24 hours for a total of 3,328 treatment days. The outcome in Kuwait. We report that.

**Conclusions:** Hypophosphatemia occurred frequently, and the incidence peaked at day 1. Although there is no ideal protocol about how to replace phosphate, our findings suggest that replacement should begin early after initiation of CRRT.

**Funding:** Veterans Affairs Support

### PO0205

**AKI in Kuwait: Incidence, Causes, Management, and Outcomes – A Prospective Observational Study**

Ali AlSahow,1 Anas M. Al Yousef,2 Bassam A. Alhelal,1 Heba Al Rajab,3 Ahmed Alqallaf,4 Yousif Bahbahani,2 Mohther M. Alsharkekh,2 Basem Said,2 Mohamed A. Osman,4 Ahmed M. Mazroue,2 Ali S. Abdelzaher,2 Alaa T. Abdelmeteleb,2 Gannal Nessim,2 Emad Abdallah,2 Rajeez K. Malhotra.4

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**Background:** Little is known about AKI epidemiology, causes, management and outcome in Kuwait. We report that.

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116
Methods: Demographics, comorbidities, treatment and 4 weeks outcome data for nephrology referrals for AKI in 7 public hospitals from 1 Jan-30/Apr/2021 prospectively collected and analyzed

Results: Total number of AKI referrals was 1298, that is 3.3% of hospital admissions.
Community acquired cases were 12.5%. Males were 55%, mean age 64 (52% > 65), and mortality was 19.4%. DM affected 71.7%, HTN 74%, and cardiac disease 25% of patients. Mean baseline eGFR before AKI was 62. Baseline eGFR < 60 seen in 52%, and those compared to patients with eGFR > 60, had mean baseline eGFR of 35 (vs 90), were older (68 vs 60 with 61% above age 65 vs 41%), 81% had DM (vs 60%), 85% had HTN (vs 74%), lower eGFR (vs > 3.0mg/dl), lower eGFR group, IV diuretics in 61% lower eGFR group, IV vasopressors in 40% (less in lower eGFR group) and steroids in 33%, KRT needed in 33%, more in patients who used diuretics or vasopressors. Volume overload and electrolytes / acid-base disorders were most common indication (75% and 79% respectively). CRRT was modality of choice in 85%, however, in 52% of CRRT, conventional HD was not used due to lack of dialysis solution in some sites. At 30 days, mean eGFR was 42%, with complete recovery in 34%, and 38% failed to recover at all. Death occurred in 31%, 55% had baseline eGFR > 60, and 50% of deaths occurred while on KRT. Non-survivors were older and had higher use of vasopressors. AKI associated mortality in 25% of total hospital mortality and in 31% of ICU / CCU mortality.

Conclusions: AKI is common. Most cases hospital-acquired. Use of resources (medications, critical care, KRT) and rates of mortality are high. Kuwaiti citizens represent 1/3 of the population and 2/3 of AKI cases and almost 70% of deaths.

PO0206
AKI in the Month of Ramadan
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Background: Fasting in Ramadan from dawn to sunset is one of Islam’s 5 pillars. Islamic lunar calendar is 11 days shorter than Gregorian solar calendar, so the start of Ramadan changes every year and hours spent on fasting vary from 12 hours in Australia, to 21 hours in Sweden, with most countries have 11-16 hours of fasting on average. Patients with certain medical illness are exempted from fasting, however, many such patients use platelet transfusion during fasting. The long hours of fasting may be a risk factor for AKI in certain populations. We assess AKI in Ramadan.

Methods: Demographics, comorbidities, treatment, and 4 weeks outcome data for all AKI referrals for nephrology consultation in AKI in 4 public hospitals in Kuwait during Ramadan of 2021 (13/4-May 2021) prospectively collected and analyzed. We compare AKI in people fasting prior to admission to non-fasting.

Results: Total number of AKI cases in Ramadan was 158, 55% males, mean age 64, and 61% were Kuwaiti citizens. Community acquire cases were 15%. DM affected 75%, HTN 72%, and cardiac disease 25% of patients. Median baseline eGFR before AKI was 66.5. Baseline eGFR < 60 seen in 43%, and those compared to patients with eGFR > 60, had median baseline eGFR of 37.5 (vs 92), were older (69 vs 62), 87% had DM (vs 68%) and 87% had HTN (vs 61%). Cause of AKI was pre-renal / ischemic AKI in 75%, 3.0% of patients, CTCAO 3.0%, COVID-19 related in 2.5%, and drug-induced AKI in 5% of cases. Many had more than one possible cause. Sepsis was most common precipitating factor seen in 67% then volume depletion in 50%. Many had more than one factor. Emergency hemodialysis was performed in 46% (vs 25% lower eGFR group), IV diuretics in 61% (vs 40% lower eGFR group), IV vasopressors in 40% (less in lower eGFR group) and steroids in 33%, KRT needed in 33%, more in patients who used diuretics or vasopressors. Volume overload and electrolytes / acid-base disorders were most common indication (75% and 79% respectively). CRRT was modality of choice in 85%, however, in 52% of CRRT, conventional HD was not used due to lack of dialysis solution in some sites. At 30 days, mean eGFR was 42%, with complete recovery in 34%, and 38% failed to recover at all. Death occurred in 31%, 55% had baseline eGFR > 60, and 50% of deaths occurred while on KRT. Non-survivors were older and had higher use of vasopressors. AKI associated mortality in 25% of total hospital mortality and in 31% of ICU / CCU mortality.

Conclusions: AKI is common. Most cases hospital-acquired. Use of resources (medications, critical care, KRT) and rates of mortality are high. Kuwaiti citizens represent 1/3 of the population and 2/3 of AKI cases and almost 70% of deaths.

PO0208
An Analysis of Risk Factors for AKI in Patients with Decompensated Cirrhosis: A 4-Year Retrospective Study, 2012-2015
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Background: Acute kidney injury (AKI) is a common complication in advanced liver disease and a significant cause of AKI in patients with decompensated cirrhosis (DxC). In this study, we sought to identify the risk factors for AKI in patients with DxC.

Methods: We conducted a retrospective analysis, which was a 4-year study involving 945 patients with DxC. AKI was diagnosed as AKI stage 2 or more. Risk factors were compared using multivariate logistic regression analysis. The model of DxC was used to determine the association between predictors and primary outcome, and Akaike information criterion (AIC) was used to select the best model. Model validation was done using bootstrap method. Primary outcome assessed was AKI stage 2 or more.

Results: The incidence of AKI in decompensated cirrhosis was 17.7%. Compared with patients without AKI, patients with AKI had higher white blood cell (WBC) count, longer prothrombin time (PT), higher total bilirubin (TBil), higher serum creatinine (SCr) and higher blood urea nitrogen (BUN), but having lower alanine aminotransferase (ALT), albumin, lower cholesterolemia (ChE), lower estimated glomerular filtration rate (eGFR), lower total cholesterol (TC), lower triglyceride (TG) and lower serum sodium concentration. But no significant differences in platelet (PLT) count among different groups. The multivariate logistic regression analysis showed that platelet counts and SA-AKI rates in a large VA database of patients with methacillin-resistant Staph aureus (MRSA) bacteremia.

Conclusions: We observed that hypertension, upper gastrointestinal bleeding, Scr, word BVC count, length of PT and eGFR were independently associated with the development of AKI in patients with decompensated cirrhosis. It is therefore, necessary to apply early intervention in patients with the risk of AKI.

PO0209
Admission Platelet Count Is an Independent Predictor of AKI
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Background: Thrombocytopenia is a recognized marker of disease severity that is associated with higher mortality in patients with sepsis-associated acute kidney injury (SA-AKI). It is plausible that thrombocytopenia is also a predictor of SA-AKI development due to the characteristic microvascular dysfunction seen in this disease state, but human studies are lacking. In this analysis, we evaluated admission platelet counts among patients with SA-AKI in a VA database of patients with methicillin-resistant Staph aureus (MRSA) bacteremia.

Methods: We evaluated patients admitted to 124 VA Hospitals who developed MRSA bloodstream infections during a hospitalization from 2007-2014. Patients were excluded if platelet counts or creatinine values were not available on 2 or more consecutive days. Predictive variables were platelet counts <150 and <100 at admission. Primary outcome was the development of in-hospital AKI, defined as a platelet increase of 0.3 mg/dL over 48 hours, or an increase of 1.5x baseline within 7 days. Cox proportional hazard modeling was used to determine the association between platelet counts and risk of AKI. Covariates were chosen using forward stepwise regression. Potential covariates evaluated for inclusion were age, race, admission laboratory values, comorbidities, antibiotic agents, infection location, healthcare utilization prior to admission, and surgical intervention, among others.

Results: A total of 6,765 patients were included, of which 2,656 (39.3%) developed AKI during admission. At admission, 1,633 (24.1%) and 757 (11.2%) had platelet counts <150 and <100, respectively. AKI rates in these patients were 44.1% and 46.2%, respectively. Platelet counts <150 and <100 were associated with 1.7 times (CI 1.07-1.28) in patients with platelet counts <150 and 1.24 (CI 1.10-1.39) in patients <100.

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Conclusions: Platelet counts of <150 and <100 at admission were found to be independent predictors of subsequent SA-AKI development in a large database of patients with MRSA bacteremia. These findings may inform future studies in the prevention and prediction of AKI development.

PO0210

AKI!Now: Defining Excellence in the Prevention of and Care for Patients with AKI

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Background: ASN is committed to define excellence in AKI prevention and care to transform management, reduce morbidity, mortality and improve long-term outcomes. AKI!Now addresses a set of well-defined objectives to achieve those goals.

Methods: The AKI!Now initiative has developed a broad education program that bridges the continuum from basic investigation to clinical studies focused on early recognition, intervention, and effective therapies with a patient-centered focus.

Results: Workgroups and tasks: Basic Science: AKI-Specific Early Interventions: Leverage basic science discoveries to innovate in AKI prevention, diagnosis, and treatment; develop a centralized research portal; promote AKI research and translational initiatives; create a roadmap to facilitate discovery and novel interventions; and enhance communication within the community.

AKI Recognition and Clinical Interventions: Artificial Intelligence (AI): Design fair and equitable AI tools among physicians and researchers; and provide expert input on pathways to implement AI tools in all clinical contexts.

Poster-AKI Recovery: Identify mechanisms of repair to identify treatment strategies to accelerate recovery; prevent adverse outcomes and identify areas of priority research; promote comparative effectiveness research benchmarks; develop, test, and promote strategies to build capacity for post-AKI care.

Public Awareness and Education: Leverage existing and develop novel education processes for health professionals and patients and multiple resources including the AKI!Now Compendium, focusing on AKI recognition, management, and recovery; collaboratively emphasize the role of continuous quality improvement in AKI recognition and care, and include patients and families in the healing process.

Conclusions: AKI is common, serious, under-recognized across the life span, and associated with severe risk of progressive adverse outcomes. Education at all levels; use of AI to improve pattern recognition, prevention, and management; development of novel specific therapies through better understanding of AKI mechanisms; and appropriate post-AKI recovery care will alleviate the severe short- and long-term individual and societal AKI impacts.

PO0211

Diagnosing and Staging AKI in the Absence of a Baseline Serum Creatinine Value

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Background: AKI is commonly diagnosed and classified from changes to serum creatinine according to the 2012 KDIGO criteria. When baseline creatinine is missing, the guideline recommends to back calculate it from an assumed MDRD-GFR of 75ml/min/1.73m2. We describe an alternative method.

Methods: From NHANES 2015-2018 data we calculated distribution of serum creatinine values for the adult US population as a whole, and for gender, age and weight subgroups. We then assessed mean values in an external validation cohort (NHANES 2011-14) for performance to predict baseline creatinine in comparison to back calculated MDRD-GFR values.

Results: Relative differences between back calculated MDRD and measured creatinine values in the validation cohort show a median bias of +8% and an interquartile precision range of 0% to +26% (Fig 1). Accuracy is rather low, with P15 and P30 values at 42% and 71%. In contrast, our gender/age-based estimation eliminates bias to 0% and improves precision, interquartile range of -6% to +13% (Fig 1). P15 increases to 58%, P30 to 86%. The relative differences show a clear age dependency for MDRD, that is not present in our gender/age-based estimation (Fig 2). Adding weight categories did not significantly improve our predictions.

Conclusions: We describe a simple method to estimate missing baseline creatinine values for assessing acute kidney injury. Compared with the current standard approach our method shows no bias, more precision and improved accuracy in predicting baseline creatinine on a population level.

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118
Pittsburgh, PA
1West Virginia University, Morgantown, WV; 2University of Pittsburgh, Provider Acceptance of Electronic AKI Alerts in a Cardiac Surgery ICU
AKI: Epidemiology, Risk Factors, and Prevention
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Background: Clinical guidelines for risk stratification of acute kidney injury (AKI) do not fully consider changes in characteristics of serum creatinine that may be informative for future risk of adverse outcomes. Identification of patient groups that display distinct patterns in trajectory of SC during an AKI may enhance risk stratification.

Methods: Latent trajectory model identified trajectory patterns of SC in a cohort of United States Veterans hospitalized with AKI. Trajectories and outcome profiles were used to establish AKI phenotypes. Risk factors for phenotypes were examined, and phenotype discrimination in short-term outcomes was assessed vis-à-vis KDIGO stages.

Results: In a cohort of 360,568 US Veterans with a hospitalization with an AKI, we identified 6 phenotypes representing distinct patterns in trajectory of SC during hospitalization. Compared to a trajectory with mild changes in SC (59.4% of cohort), moderate (23.1%), and more severe changes (8.7%) with moderate recovery were associated with decreasing odds of non-recovery in SC by discharge (OR=0.52 and 0.23 respectively), higher odds of receipt of kidney replacement therapy (KRT) (3.8 and 0.62), and death within 30-days of hospitalization (1.8 and 2.5). Those whose SC continued to rise during hospitalization (3.86%) had the lowest odds of recovery (OR=0.02) and highest odds of mortality (8.0). Phenotype with highly increased SC with incomplete recovery (2.81%), or very dynamic change in the first few days of hospitalization (2.15%), were associated with higher odds of KRT (57.3 and 89.4, respectively) and lower odds of recovery (0.08 and 0.11). A prior history of chronic kidney disease, albuminuria, and prior AKI, as well as major in-hospital events including sepsis, admission to ICU, and mechanical ventilation, were associated with trajectories with worse outcomes. Discrimination in future outcomes during course of hospitalization suggested that as the hospitalization progressed, phenotypes increasingly provided more information on risk of future outcomes (C-statistic: 0.72, recovery; 0.97, KRT; 0.62, death) than KDIGO stages (0.02, recovery; 0.75, KRT; 0.59, death).

Conclusions: Our results suggest that leveraging EHR data to profile changes during the occurrence of AKI in kidney function may enhance risk stratification of AKI patients during the course of hospitalization.

Funding: Veterans Affairs Support, Private Foundation Support

PO0203
Phenotyping Inpatient AKI by Serum Creatinine Trajectory
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Introduction: AKI: Epidemiology, Risk Factors, and Prevention
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2 Steve Goodiwn,1 Rebecca J. Mullett,1 Gordon S. Smith,1 John A. Kellum.2
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Background: Electronic acute kidney injury (AKI) alerts can improve the rates of detection of AKI, though their effect on improving patient outcomes has been variable. Their focused utilization in cardiac surgery patients, a population at a high risk for both AKI and its complications, is likely to lead to more consistent improvement in outcomes. We implemented AKI alerts in the cardiac surgery ICU of a tertiary care, high volume cardiac surgery center starting July 2020. As electronic alerts can be disruptive to the workflow and lead to alert fatigue, we surveyed health care providers in our cardiac surgery intensive care unit (ICU) regarding their acceptance of these electronic AKI alerts.

Methods: Our AKI alerts used a previously validated logic to trigger an alert when serum creatinine increase by 0.3mg/dL or more within last 52 hours. They were implemented as passive alerts in the EPIC electronic medical record. Alerts were situated in the inpatient storyboard and provided information in the format “Possible AKI Stage X”, with the option to get more information by hovering over the alert. The alerts were set to disappear if no further increase in creatinine by at least 0.3mg/dL was noted in next 52 hours. We emailed a validated survey regarding alert usefulness to providers 6 months into the alerts implementation to assess their acceptance.

Results: Out of 19 ICU providers (7 intensivists and 12 advanced practice providers) all but one responded to the survey. 7/18 (38.8%) providers reported that they recognized AKI earlier due to the alert. 16/18 (88.9%) shared that they re-dosed or discontinued medications earlier due to the AKI alert. Majority of participants also reported erleases management of volume status (72.2%), avoidance of iv contrast use (72.2%) and point of care ultrasound use (77.8%) in response to the alert. 15/18 (83.3%) of providers reported satisfaction with the way AKI alerts are displayed and overall satisfaction with the AKI alerts. 16/18 (88.9%) providers reported satisfaction with the duration the alert is displayed for.

Conclusions: Among providers taking care of patients at high risk for AKI, the electronic AKI alert well received. A follow up survey is planned to assess the changes in longitudinal perception of the AKI alert.

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PO0215
Kratom, an Herbal-Induced Cholestatic Liver Failure, Leads to Cholemic Nephropathy Requiring Liver Transplant and Hemodialysis
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Introduction: Kratom, an herbal supplement, has opioid-like and stimulant effects. Its national misuse has increased in the United States (US). Its alkaloid content consist primarily of mitragynine and 7-hydroxymitragynine and are metabolized in the liver. Reports have shown many side effects, notably confusion, seizures, coma, and hyperbilirubinemia. Hepatic injury presents as cholestatic liver injury, which has a consequence on renal function. Patients with hyperbilirubinemia, bile casts damage the nephron directly and is known as bile cast nephropathy, a rare or undiagnosed pathology. We present a case of Kratom usage that play a role in causing cholestatic liver failure, leading to cholemic nephropathy and liver transplant and hemodialysis.

Case Description: A 26-year-old woman with history of Kratom usage presented with complaint of 5-days of abdominal distention and pain, jaundice, and heavy mucosal bleeding. Laboratory testing revealed Na+ 123 mmol/L, BUN 84 mg/dL, Cr. 6.9 mg/dL, AST 104, ALT 31, total bilirubin 32 mg/dL and ALP 124 units/L, WBC 27.8, platelets 109, and H/O 7.2:20.7, INR 2.23. There was no serology evidence of viral infection. Tylenol and alcohol level were unremarkable. Urinalysis positive for bile acid cast. Abdominal ultrasound and Computed Tomography findings are consistent with liver cirrhosis. She underwent liver transplantation and required hemodialysis due to acute renal failure from profound hyperbilirubinemia.

Discussion: Bile cast nephropathy represents a wide spectrum of disease, ranging from mild reversible to irreversible needling dialysis. It occurs when total bilirubin levels >20mg/dL, exceeding the binding capacity of albumin to bilirubin. It causes tubular obstruction and injury, oxidative damages, and ATPasence. Most of the damage occurs in distal tubules but can occur in the proximal tubules. While Kratom has stimulant and opioid-like effects, its use can be hazard to health. There currently no treatment guidelines for bile cast nephropathy. In irreversible nephropathy in cirrhotic patient, patient may be evaluated for both liver and kidney transplant. Renal replacement therapy has no role in treating bile cast nephropathy. Hence the nephrology team should keep cholemic nephropathy as a differential diagnosis in patient with hyperbilirubinemia and be aware of the increasing consumption of kratom in the US.

PO0216
Dietary Hyperuricemia Causes Nephropathy in a Cancer Patient
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Introduction: Hyperuricemia is associated with several diseases including kidney disease. Everyday drinks (sodas/juices) have very high fructose content, contributing to hyperuricemia through various mechanisms. Here we report a case of a cancer patient with Acute Kidney Injury (AKI) secondary to hyperuricemia in the setting of a sudden high intake in fructose rich drinks.

Case Description: A 49-year-old Asian man with history of myeloidoblast, coronary artery disease and chronic kidney disease stage 2, was admitted for AKI. He was recently admitted for septic shock due to scrotal abscess and discharged to a nursing home for wound care. He endorsed recent high intake of sodas and juices, due to dislike of food at the nursing home. His creatinine at previous admission was 1.1–1.4 mg/dL (similar with his background intake). His urinalysis (UA) routinely did not show uric acid crystals, and uric acid levels were within reference range. One week prior to admission, his creatinine was 1.97 mg/dL and UA showed occasional uric acid crystals. At current admission, creatinine was 3.02 mg/dL with uric acid level of 23.3 mg/dL, and UA showed uric acid crystals. He was treated with 3 doses of 3 mg Rasburicase (9 mg total) the first day, after which uric acid level improved to 6.4 mg/dL, and creatinine dropped to 2.14 mg/dL. Three days later his creatinine improved to 1.76 mg/dL, and repeat UA did not show uric acid crystals. A week after discharge, his creatinine was at baseline and uric acid level was normal. By the time visual examination of urine with uric acid crystals. A week after discharge, his creatinine was at baseline and uric acid level was normal. By the time visual examination of urine with uric acid crystals. A week after discharge, his creatinine was at baseline and uric acid level was normal. By the time visual examination of urine

Discussion: It is known that fructose is the only carbohydrate that increases uric acid levels. Fructose-induced hyperuricemia results from an increased degradation of purine ribonucleotides and causes increased purine synthesis. Hyperuricemia is common in patients with hematologic malignancies with or without chemotherapy. Our patient had a hematological malignancy and endorsed drinking large amounts of soda and juice. Given many patients drink fructose rich drinks daily, it is imperative that the dangers of this dietary habit are highlighted, both to physicians and patients. Cancer patients can benefit from nutrition education and dietary modifications prior to and during chemotherapy to prevent hyperuricemia and in turn should help avoid need for hospitalization as well as use of expensive uric acid lowering agents.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

119
Turmeric-Associated Oxalate Nephropathy
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Introduction: Turmeric contains Curcumin which has anti-inflammatory properties that may be beneficial in patients with osteoarthritis, hyperlipidemia, pruritus, and Rheumatoid Arthritis. Thus it’s a popular herbal supplement. Here we present a rare case of severe acute kidney injury (AKI) due to calcium oxalate nephropathy in a patient with heavy turmeric consumption.

Case Description: An asymptomatic 69 year male with no significant past medical/surgical history was evaluated for a spike in Creatinine from 1.2 to 3.1 mg/dl over a few months. There was no history of drug/NSAID use, contrast exposure, or other nephrotoxins. He did mention taking Turmeric 2g daily for the past 2 years. There was no personal or family history of nephro lithiasis. Urine sediment was bland. Serum C3, C4, ANA, ANCA, anti-GBM, anti-dsDNA, hepatitis B&c screen, SLEKUP/EPEP were negative. Kidney Biopsy revealed widespread calcium oxalate deposition in tubules(Renal Oxalosis-Hyperoxaluria) with diffuse acute tubular injury. Turmeric was discontinued, but the patient soon started on dialysis. 24h urine oxalate was elevated; serum oxalate was also high at 14 micromol/L. Genetic testing (AGXT mutation) for primary hyperoxaluria(PH) is pending, but lack of recurrent nephro lithiasis or nephrocalcinosis or systemic oxalate deposition and only marginally high S.oxalate make PH less likely.

Discussion: Although many herbal remedies have shown promising results, these supplements often evade the rigorous standards that conventional therapies are subject to. Turmeric has long been used for anti-inflammatory & analytic benefits and recently was publicized as an immunity booster and studied for prophylactic and therapeutic use in COVID. Compelling evidence for its efficacy comes from osteoarthritis trials, but recommendations for safe daily allowances aren’t elucidated. Contrarily, turmeric has demonstrated increased urine oxalate excretion, a known cause of stone stones and presumably, oxalate deposition in tubules. Hyperoxaluria mainly occurs secondarily in malabsorption syndromes. Loss of oxalate-degrading gut flora from antibiotics contributes and PH, a disorder of oxalate overproduction, is a rare cause. Several factors can interplay, but the contribution of oxalate-rich food like spinach, starfruit, and in this case, turmeric is indisputable. We recommend a high suspicion index and a thorough medication review in patients with severe AKI.

PK00217

AKI: Epidemiology, Risk Factors, and Prevention
Poster

Ultimate survival in AKI is highly dependent on renal function. Several factors are independent predictors of AKI in hospitalized patients. The aim of this study is to determine the use of combination of BUN and tryptophan could improve mortality risk prediction in early time-point in trauma-induced model.

Methods: In a prospective cohort study, we determined serum tryptophan and BUN levels in ICU patients with severe AKI. Tryptophan levels were determined using a sensitive and specific amino acid assay. Multivariate logistic regression analysis was employed to quantify the association of survival with the metabolite concentration. The group with increased tryptophan concentration had a better chance of survival than the group with a reduction of tryptophan from the baseline. Survival analysis indicated that a decrease in serum tryptophan level is an independent predictor of mortality. Conclusions: It is the first study to report the association between tryptophan levels and mortality in ICU patients with severe AKI. These findings have important implications for the development of new therapeutic strategies to improve outcomes in patients with severe AKI.

Interaction of Blood Urea Nitrogen and Tryptophan in Predicting Mortality in a Trauma-Induced Model
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Background: Multiple organ failure (MOF), often precipitated by Acute Respiratory Distress Syndrome (ARDS) brought on by trauma-induced injury, is a significant cause of death in military and civilian life. Furthermore, in ARDS, Acute Kidney Injury (AKI) is the most frequent organ failure affecting almost 50% of the patients, increasing the mortality rate. Therefore, understanding the molecular difference between survivors and non-survivors is critical for improving survival rates.

Methods: A porcine MOF model (n=17) was developed using pulmonary contusion injury at Dr. Batchinsky’s laboratory. In this model, n=10 are survivors, and n=7 are non-survivors with mortality at 3, 6, and 9 hours. Serum was employed for Amino acid analysis using the Zip-Strip platform for mass spectrometry. A Cox proportional hazard analysis was employed to quantitate the association of survival with the metabolite concentration. Serum blood urea nitrogen (BUN) was measured using the assay kit, and baseline BUN was correlated with baseline tryptophan level using a linear model.

Results: In survival analysis, survivors and non-survivors were partitioned by the mean metabolite concentration. The group with increased tryptophan concentration had a better chance of survival than the group with a reduction of tryptophan from the baseline. Furthermore, when associating the tryptophan level with the BUN, there is an opposite trend between the two groups. In the survivors, higher tryptophan is positively associated with increased BUN, whereas in the non-survivors, there is a negative correlation indicating that lower tryptophan coupled to high BUN increases the risk of mortality. Additionally, linear regression model showed a significant association of tryptophan and BUN with survivors and non-survivors.

Conclusions: Survival analysis indicated that a decrease in serum tryptophan level is a strong risk factor for mortality. Since tryptophan metabolism is associated with renal failure in AKI settings, we investigated serum tryptophan association with BUN. Non-survivors have a strong negative association of tryptophan with BUN, suggesting that combination of BUN and tryptophan could improve mortality risk prediction in early time-point in trauma-induced model.

Funding: Other U.S. Government Support

BK Polyomavirus Nephritis in a Low-Risk Native Kidney: A Case Report
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Introduction: BK viremia has increased prevalence in solid organ transplant, particularly renal transplant recipients. BK nephropathy in native kidney is rare, but has been reported after hematopoietic stem cell transplant (HSCT).

Case Description: 24-year-old male with Grade 2 Follicular lymphoma (in complete remission for 2 years after infusimotuzumab, bendamustine, & venetoclax), complicated by hypogammaaglobulinemia receiving IVIG (IgG 751mg/dl) & chronic lymphopenia (absolute lymphocyte 152 cells/ul) who was evaluated for acute kidney disease. Patient’s baseline creatinine was around 0.8 mg/dl & progressively rose to 4mg/dl over a period of 6 months despite IV hydration for intermittent mild diarrhea. Urinalysis had no proteinuria or hematuria. Serologic workup for systemic lupus erythematosus and other autoimmune disease, monoclonal gammopathy, sarcoid was unrevealing. Kidney biopsy revealed polyomavirus nephritis with acute tubular injury & severe interstitial fibrosis with tubular atrophy. Serum BK PCR showed 1.3 million copies. The patient continued on IVIG increasing the frequency to every 3 weeks and started on a course of fluoroquinolones but with ultimate progression to chronic kidney disease.

Discussion: BK virus infections in immunocompetent individuals typically occur early in childhood (asymptomatic or mild respiratory illness). Following primary infection, BK virus remains in a latent state in the urothelium & renal tubular epithelial cells. Most cases of BK Polyomavirus nephritis occur in renal transplant recipients. BK Polyomavirus nephritis in native kidneys include non-tubular organ transplant as well as HSCT, chronic lymphocytic leukemia, AIDS, and congenital dysgammaglobulinemia. Clinical presentation is nonspecific and includes varying degrees of renal failure without fever, leukocytosis, hematuria or proteinuria. Incidence of BK viremia is dependent on the degree of glomerular inflammation caused by proinflammatory cytokines, influx of immune effector cells, BK virus lytic replication, and lysis of renal tubular epithelial cells that can lead to renal fibrosis. Treatment agents include leflunomide, cidofovir, fluoroquinolones and IVIG but the success has been limited. This case highlights that BK Polyomavirus nephritis may develop in the native kidney other than HSCT. Chronic lymphopenia & hypogammaglobulinemia likely predisposed our patient despite his ongoing infusion of IVIG.
Performance of Validated Indices for Risk of Death for Patients with AKI Requiring Dialysis: A Systematic Review and Meta-Analysis

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Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high morbidity and mortality. Multiple mortality indices have been developed, however, the most optimal index for predicting survival in AKI requiring RRT is unknown. Objective: To assess performance of validated mortality indices for patients with AKI requiring RRT.

Methods: Design, setting, participants and measurements: Systematic review and meta-analysis following the PRISMA guidelines. Multiple databases (MEDLINE, Embase, Central Register of Controlled Trials, Cochrane, and Scopus) were searched from inception to Jan 31 2019. Selection Criteria: Studies evaluating the performance of validated mortality indices in adult AKI patients requiring RRT were included. Studies not separating AKI patients requiring RRT or used validated indices only as covariates were excluded. Articles were screened and data extracted in duplicate. Risk of bias was assessed using the PROBAST tool. Pre-planned random effects meta-analysis was performed stratified by index, population, renal specific vs. general mortality index, and predictive window.

Results: Of 10,115 articles screened, 37 (2 development, 21 validation and 4 combined) were included totaling 35 different indices tested in 11,142 patients. Average age was 60.8 years with 54.6% women. Predictive windows ranged from ICU to 60-day survival. The most used indices were APACHE II, Liano, SOFA, and SAPS II. Meta-analysis by index showed overall discrimination area under the curve (AUC) of 0.69 (95% CI 0.67-0.71) with high heterogeneity (I² =82.8%) with highest AUC for APACHE III (0.73-0.78) and MODS 0.71(0.62-0.80).

Conclusions: There is insufficient discrimination and heterogeneity in the performance of prognostic indices for AKI requiring RRT. Additional studies are needed to optimize mortality prediction in this population.

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Detection and Diagnosis of AKI in the Emergency Department

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Background: Acute kidney injury (AKI) represents an abrupt decline in kidney function occurring over hours or days and is associated with inferior clinical outcomes. In recent years, new definitions of AKI based on changes in serum creatinine (SCr) have gained acceptance, but awareness by primary care and emergency physicians may still be limited. The aim of this study was to use diagnosis codes to examine the detection of AKI among patients admitted to the emergency department (ED).

Methods: This was a prospective case-control study in which SCr of all individuals measured at each patient once daily till 7th day. The results were presented as a mean value (Cr); glomerular filtration ratio (GFR), serum activity of asparagine transaminase (AST) and creatinine (Cr); glomerular filtration ratio (GFR), serum activity of asparagine transaminase (AST) and creatinine (Cr)

Conclusions: Biochemical symptoms of AKI were confirmed in 15 (60.6%) pts. AKI was associated with renal symptoms. The significant relationship between parameters and the characteristic level of an epidemiologic pattern on ICU patients for future applicability.

Funding: Government Support - Non-U.S.
PO0225

Intravenous Administration of Vitamin B Complex Improves Renal Recovery in Patients with AKI
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Background: Preclinical studies have identified NAD+ augmentation as a potential strategy for the prevention and treatment of AKI. NAD+ is the final metabolized form of vitamin B3 (niacin). Since there is no availability of niacin in the country; we tested if IV vitamin B complex (vitamin B1, B6 and B12) could improve renal recovery in patients with AKI. By oxidation, vitamin B6 (pyridoxine) through the pathway of pentose phosphate lead to the formation of NADPH in an analog of NAD+.

Methods: We conducted randomized, blind, placebo-controlled study in hospitalized patients with AKI (NCT04893733). During the study IV vitamin B complex or placebo was given twice a day for 5 consecutive days. For AKI management in each patient, a protocol-based approach was used (STOP AKI protocol from the ISN 0by25 trial https://doi.org/10.1371/journal.pmed.1003408). We evaluated if vitamin B complex could improve renal recovery and if it could reduce de novo CKD incidence or CKD progression.

Results: From September 2020 to May 2021, 191 patients were enrolled in this ongoing RCT with 160 patients completing the follow-up by day 7 and 91 patients completing the follow-up by 3 months. Peak sCr was higher in patients randomized to vitamin B complex (2.8 ± 1.2 vs. 2.2 ± 1.3 mg/dl; p = 0.006). A higher percentage of patients randomized to vitamin B complex arm had severe AKI (stage ≥ 2) 74% vs. 45% randomized to placebo; p = 0.011. The drop in sCr values by day 7 was higher in the vitamin B complex group (1.01 vs. 0.65 mg/dl; p < 0.001). No differences were found in the percentage of patients with complete recovery (54.3% vs. 45.6%; p = 0.268), partial recovery (25.9% vs. 25.3%; p = 0.930) and non-recovery (19.8% vs. 29.1%; p = 0.168). At 3 months, the incidence of de novo CKD and CKD progression was not different in both arms (23.9% vs. 20%; p = 0.652 and 28.2% vs. 26.6%; p = 0.865 respectively). No difference was found in mortality rate at day 90 (vitamin B complex 31.1% vs. placebo 28.2%; p = 0.544).

Conclusions: The administration of vitamin B complex could potentially accelerate renal recovery in patients with AKI by day 7, reducing the percentage of patients who will not recover renal function after an AKI episode. No differences were found in terms of CKD progression or de novo CKD. The preliminary data of our ongoing study warrants future studies to validate these findings.

PO0226

GDF-15 Predicts In-Hospital Mortality of Critically Ill Patients with AKI Requiring Continuous Renal Replacement Therapy: Results from a Prospective Randomized Controlled Trial
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Background: Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine that is positively associated with inflammation. This study evaluated the association between GDF-15 and in-hospital mortality among patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: Among the multicenter prospective CRRT cohort between 2017 and 2019, 66 patients whose blood sample was available were analyzed. Patients were divided into three groups according to the GDF-15 concentrations. In-hospital mortality was compared using Cox proportional hazards regression model.

Results: The mean age was 67.7 ± 14.3 years and 47 (71.2%) were male. The median GDF-15 level was 7865.5 pg/mL (496.9 pg/mL in the healthy control patients). Baseline characteristics were not different among tertile groups except the severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and Sequential Organ Failure Assessment [SOFA]) and serum lactate level, which were higher in the third tertile. After adjusting for confounding factors, the patients with higher GDF-15 had significantly increased risk of mortality (second tertile: adjusted hazards ratio [aHR], 3.67; 95% confidence interval [CI], 1.05–12.76; P = 0.041; third tertile: aHR, 6.81; 95% CI, 1.98–23.44; P = 0.002). Furthermore, GDF-15 predicted in-hospital mortality (area under the curve, 0.710; 95% CI, 0.585–0.815) better than APACHE II and SOFA scores (Figure 1).

Conclusions: Serum GDF-15 concentration was elevated in AKI patients requiring CRRT, higher in more severe patients. GDF-15 is a better independent predictor for in-hospital mortality of critically ill AKI patients than the traditional risk scoring system such as APACHE II and SOFA scores.
Restriction of Sulfur-Containing Amino Acid Intake for Prevention of AKI in Cardiac Surgery: UNICORN, a Randomized, Controlled, Double-Blinded Trial

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Background: Acute kidney injury (AKI) can result in short- and long-term complications and increased mortality. Nonetheless, preventive and therapeutic strategies are lacking. Protein restriction has been shown to protect from organ failure in mice and this protection depended on restriction of sulfur-containing amino acids (SAA). The UNICORN study aims to evaluate the impact of restricting SAA intake by replacing milk-derived dietary protein by collagen prior to cardiac surgery on AKI.

Methods: In this single-center, randomized, controlled, double-blinded trial 115 patients scheduled for cardiac surgery, were assigned in a 1:1 ratio into a LowS group (SAA depleted formula diet) or a regular formula diet (control group, CG) for 7 days prior to surgery. The primary endpoint was incidence of AKI within 72 hours after surgery (KDIGO), secondary endpoints included increase of serum creatinine at 24h, 48h and 72h as well as safety parameters. Quantitative variables were analyzed with t-test or nonparametric methods, while categorical variables were evaluated by means of Chi-Square or Fisher’s test.

Results: Baseline characteristics: LowS serum creatinine 1.0 mg/dl[0.34] vs. CG 0.85 mg/dl[0.42]; LowS 77% male vs. CG 54%; age: LowS 67y[12] vs. CG 69y[12], body weight: LowS 88 kg[20] vs. CG 78kg[18], crossclamp time: LowS 67min[32] vs. CG 68min[35]. Patients in the LowS group had a 77.6% reduction in SAA as compared to CG. There was no difference in the primary endpoint between the groups (LowS AKI incidence 23% vs. CG 16%; p=0.37). Likewise, no differences were observed with respect to secondary endpoints (AKI during hospitalization, creatinine at 24h, 48h, 72h after surgery). Subgroup analysis focusing on age, gender, body mass index and markers of organ damage did not reveal any significant differences.

Conclusions: In this first-in-humans translational clinical trial, dietary SAA restriction before cardiac surgery did not result in a lower incidence of AKI. However, larger studies are needed to confirm this finding.

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Use of Peritoneal Dialysis for the Treatment of AKI Was Associated with Lower Risk for 30-Day All-Cause Mortality During the COVID-19 Surge

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Background: To offset resource constraints that limited the capability to deliver hemodialysis (HD) during the COVID-19 surge, nephrologists in New York City (NYC) rapidly incorporated peritoneal dialysis (PD) for the treatment of acute kidney injury (AKI), which was rarely used in the United States. This study aims to compare the in-hospital all-cause mortality between AKI patients who received PD versus HD during the COVID-19 pandemic.

Methods: In a retrospective observational study, we collected data on 259 patients with AKI who required kidney replacement therapy (KRT) in four medical centers of NYC during the Spring 2020. Patients who had ever received PD were included in the PD group (n=93), and patients who only received intermittent HD or continuous KRT were included in the HD group (n=166). Kaplan-Meier survival curves, log-rank test and Cox regression were used to compare survival between PD and HD groups.

Results: For the entire cohort, the mean age was 61±11 years; 31% were women; 96% had confirmed COVID-19. Median follow up was 21 days (IQR 12-30). Mortality was lower in PD group compared to HD group (43% vs. 60%, p=0.01). Time-dependent analyses showed that PD group was at a lower risk for mortality compared to HD group (p=0.001 for log-rank test; Figure). After adjusting for age, sex, BMI, comorbidities, oxygenation on admission, mechanical ventilation, prone positioning, steroid use and C-reactive protein, the PD group remained to have a lower risk of mortality compared to the HD group with a HR of 0.45 (95% CI: 0.27-0.77; p<0.003).

Conclusions: Compared to HD, the use of PD for the treatment of AKI was associated with lower mortality in this cohort of patients treated during the COVID-19 pandemic in the Spring of 2020. Our findings demonstrate that rapid implementation of PD for the treatment of AKI was feasible and may be lifesaving.

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PO0231
Risk Factors for Long-Term Mortality Following AKI
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Background: Acute kidney injury (AKI) occurs in over 20% of hospitalized patients and is associated with increased long-term mortality. The purpose of this study is to identify risk factors for mortality following a hospitalization with AKI in US Veterans.

Methods: AKI was defined as a creatinine increase of ≥0.3 mg/dL at or after admission to a VA hospital between 2013 and 2018. The primary outcome was mortality, with follow-up ranging from 2-7 years. Over 50 variables were considered for inclusion in the final model, including demographics, comorbidities, and laboratory data. Bootstrap modeling was used to determine the outcomes of one hundred stepwise regressions using random sampling with replacement, and those included in more than 60 of the 100 models were considered in the final model using Cox regression. Given that over a quarter of post-AKI mortality is due to cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease at baseline.

Results: A total of 241,781 Veterans with AKI were included. There were 47,390 deaths at follow-up, and 40,465 deaths at follow-up in the non-cardiac group, and 54,384 deaths out of 102,637 with and without pre-existing cardiac disease at baseline. Harrell’s Concordance values were 0.67 and 0.66, respectively. Cardiac deaths out of 139,144 (34%) in the non-cardiac group, and 54,384 deaths out of 102,637 with and without pre-existing cardiac disease at baseline.

Conclusion: AKI mortality is due to cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease at baseline.

PO0233
Reduction of Intraoperative Nephrotoxic Antibiotic Exposure Can Decrease the Severity of Stage of AKI and Improve Renal Recovery in Patients Undergoing Heart Transplantation
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Background: Acute Kidney Injury (AKI) is very common complication post-heart transplant with a reported incidence of approximately 47-76%. Antibiotic combinations, such as piperacillin-tazobactam and vancomycin can cause nephrotoxicity and AKI especially in high doses. The mechanism for this nephrotoxicity is not clear. The purpose of this study was to evaluate the impact of reducing intraoperative nephrotoxic antibiotic exposure on the rate of Acute Kidney Injury and renal recovery in adult patients undergoing heart transplantation.

Methods: This is a single-center prospective study design of all adult patients undergoing heart transplants at Medical University of South Carolina between 4/12/2015 to 5/1/2020. In 06/2019, as part of a quality improvement effort to reduce our AKI rate, we changed empiric intraoperative antimicrobial coverage from piperacillin-tazobactam to cefepime while continuing vancomycin use. We collected data using the electronic health record. AKI severity and recovery were extracted for patients exposed to piperacillin-tazobactam and vancomycin or cefepime and vancomycin. AKI was identified using KDIGO serum creatinine criteria. Renal recovery was defined as 25% improvement in serum creatinine within 7 days. We assessed rates of nephrotoxin exposure and KDIGO AKI rates in all heart transplant inpatients for at least 4 years pre-intervention and almost 1 year post-intervention.

Results: While the overall rate of AKI remained the same after the intervention, the rates of severe stage 3 AKI decreased by 32%. Recovery of AKI prior to hospital discharge improved 4-fold in the intervention group (24.0% vs 6.0 %, P < 0.05). There was a trend towards less readmissions at 6 months with the intervention group (48.6% vs 64.9%, P = 0.117).

Conclusion: Reduction of nephrotoxic antimicrobial exposure can decrease the severity of heart transplant-related AKI and improve AKI recovery rates.

PO0232
The Clinical Characteristics of Inpatients with AKI and the Risk Factors for Progression to CKD
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Background: To explore the incidence of AKI in hospitalized patients and demonstrate the distributions and clinical characteristics of AKI and the risk factors for progression to CKD.

Methods: Medical records of inpatients were acquired from Nanjing Health Information Platform from January 1 to December 31, 2019. A total of 20258 patients with 2 or more serum creatinine records during one single hospitalization were enrolled. We analyzed the distribution, clinical features, and associated risk factors of AKI. A prospective cohort of 999 AKI patients was followed up for a medium of one year. Multivariable logistic regression was used to analyze the risk factors for the progression from AKI to CKD and a risk predictive model was established accordingly.

Results: Among the enrolled patients, 2194 (10.8%) developed AKI in this study. The prevalence of AKI in medical department, surgical department and ICU were 9.1%, 12.1% and 20.0%, respectively. The incidence of AKI in men and elderly in the AKI group. Patients with AKI were more likely to be complicated with diabetes, hypertension, and CKD. The baseline serum creatinine, uric acid, fasting blood glucose and inflammatory biomarker in AKI group were significantly higher than those in non-AKI group. On the contrary, those with AKI had lower blood lipids, albumin and hemoglobin. The presence of AKI predicted a significant increase in hospitalization cost, duration and all-cause mortality. Furthermore, 110 individuals (11.0%) progressed to CKD in the prospective cohort. Age, AKI stage, hypertension, baseline serum creatinine, uric acid, lymphocyte and albumin to creatinine ratio were independent risk factors for progression to CKD. A risk predictive model of progression from AKI to CKD was established with an area under the ROC curve of 0.822 (95%CI:0.878 – 0.877, P < 0.001).

Conclusions: Age, AKI stage, baseline serum creatinine, hypertension, hyperuricemia and hypo-hemoglobinemia were independent risk factors for the progression of CKD in AKI patients. Predictive model established using these variables can help us screen these high-risk populations.

Funding: Government Support - Non-U.S.

PO0234
Clinical Trajectories of AKI in Hospitalized Patients

Background: In surgical sepsis patients, AKI trajectory subgroups have unique physiologic signatures of immunologic and endothelial dysfunction, suggesting potential utility for targeted, therapeutic interventions. It is unknown whether the same phenomena occur among all hospitalized patients. Our objectives are to understand the baseline characteristics of patients who will develop distinct AKI trajectories, determine differences in clinical outcomes, resource use, and long-term survival by AKI trajectory groups defined by persistent kidney injury and renal non-recovery on, and assess the relative importance of AKI severity, duration, and recovery on survival.

Methods: We performed a retrospective study of 156,699 patients admitted to a quaternary care academic hospital between January, 2012 and August, 2019. We used Kidney Disease Improving Global Outcomes and Acute Dialysis Quality Initiative criteria to stage AKI and classify patients as having no AKI, rapidly reversed AKI, persistent AKI with recovery, or persistent AKI without renal recovery. Clinical outcomes, resource use, and long-term survival rates were compared among AKI trajectory groups. Cox proportional-hazards regression was used to assess associations between AKI trajectories and time to death while controlling for demographics, Charlson comorbidity score, and provision of mechanical ventilation and ICU admission for two days or greater.

Results: Fifteen percent (54,212/355,678) of the encounters developed AKI. Fifty-eight percent (31,500/54,212) of AKI episodes rapidly reversed within 48 hours; among patients with persistent AKI, two-thirds (14,122/22,712) did not have renal recovery by discharge. One-year mortality was significantly higher among patients with persistent AKI (35%, 7,856/22,712) compared to patients with rapidly reversed AKI (15%, 4,714/31,500) and no AKI (7%, 22,117/301,466). Persistent AKI without renal recovery was associated with approximately five to six fold increased mortality compared to no AKI, rapidly reversed AKI, or persistent AKI without renal recovery. Clinical outcomes, resource use, and long-term survival rates were compared among AKI trajectory groups. Cox proportional-hazards regression was used to assess associations between AKI trajectories and time to death while controlling for demographics, Charlson comorbidity score, and provision of mechanical ventilation and ICU admission for two days or greater.

Conclusions: Among hospitalized patients, persistent AKI and the absence of renal recovery are associated with increased health care resource use and decreased short- and long-term survival. Early identification of patients at increased risk for persistent AKI may facilitate the provision of resource targeted treatments.

Funding: NIDDK Support
PO0235

Incidence and Prognosis of Different Stages of Acute Kidney Disease: A Single-Center Retrospective Cohort Study

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Background: The 16th Acute Disease Quality Initiative (ADQI) recommends that the definitions and staging criteria for acute kidney disease (AKD) be congruent with the stage of AKI. To delineate the prognostic values of the AKD staging system, we constructed a large retrospective cohort and evaluated the disparate outcomes among patients with different stages of AKD.

Methods: This study was a retrospective cohort study including 4,741 adult AKI patients in a single tertiary medical center from 2015 to 2018, with at least 1 serum creatinine measurement between 7 to 90 days after AKI. The 16th ADQI recommendations were used to estimate the proportion of patients at different AKD stages (Figure 1). All patients were followed up for 1 year (study end date, Dec 31st, 2019) to analyze risk factors associated with eGFR decline, initiation of dialysis and in-hospital mortality.

Results: Among the 4,741 AKI patients included in the cohort, AKD stages 1-3 after AKI was common (53% in the CKD group and 51% in the non-CKD group). In the logistic regression model adjusted for demographics and comorbidities and after a 1-year follow-up, AKD stages 1/2/3 (AKD stage 0 as reference group) were associated with higher risks of eGFR decline (AKD stage: Odds ratio, 95% Confidence Interval [95% CI], AKD 1: 2.14, 1.65-2.79; AKD 2: 2.64, 2.01-3.47; AKD 3: 2.90, 2.29-3.66), initiation of kidney replacement therapy (AKD stage: Odds ratio, 95% CI, AKD 2: 1.88, 1.39-2.53; AKD 3: 8.72, 7.07-10.76), and in-hospital mortality (AKD stage: Odds ratio, 95% CI, AKD 2: 1.88, 1.39-2.53; AKD 3: 3.23, 2.65-3.94; AKD 3: 5.59, 4.69-6.67).

Conclusions: Staging criteria for AKD identified AKI patients at higher risk of kidney function decline, dialysis, and mortality. AKD patients with a more severe stage need to receive intensified care.

Funding: Government Support - Non-U.S.

PO0237

Risk of Renal Recovery Post Dialysis-Requiring AKI in Critically Ill Transplant Patients Receiving Calcineurin Inhibitors

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Background: The use of the calcineurin inhibitors has led to major advances in the field of transplantation, with excellent short-term graft outcomes. However, these agents are associated with chronic nephrotoxicity and long-term may lead to ESRD. The purpose of this study was to assess the risk of renal recovery at 3 months in critically ill transplant and non-transplant patients who required continuous renal replacement therapy (CRRT) (AKI-D).

Methods: This is a single center retrospective study aimed to assess differences in renal recovery from AKI-D in critically ill transplant and non-transplant patients (AKI-D) in both non-transplant patients (CNI - patients) and transplant patients taking calcineurin inhibitors (CNI + patients). Our study was undertaken from 02/2017 to 07/2019 at the Medical University of South Carolina, and our analysis included 153 critically ill patients who received CRRT for AKI-D. Non-renal recovery from AKI-D was defined as ESRD as per KDIGO guidelines. We performed a Cox Hazard Risk Model to assess risk of CNI use on renal recovery at 3 months adjusted for transplant status, mortality at 28 or 90 days, age, sex, hypertension, DM, APACHE score and initial number of vasoactive medication used at that time of CRRT initiation.

Results: CNI users had 61% lower risk of developing end stage kidney disease compared to non-CNI users at 90 days (HR 0.49, p = 0.49, CI 0.07 -3.69) although this risk was not statistically significantly. Interestingly, there was a statistically significant lower rate of 28-day and 90-day mortality in the critically ill transplant AKI-D cohort (21% and 37%, p< 0.05) when compared to the critically ill non-transplant AKI-D cohort (57% and 61%, p<0.05, respectively) (see figure).

Conclusions: Even in this small retrospective cohort analysis, critically ill AKI-D patients requiring CNI agents did not have a statistically significant higher rate of ESRD despite CNI use and was associated with a lower 28- and 90-day mortality. More research is required to study the relationship between CNI use on renal recovery.

Outcomes by Transplant Recipient (Yes) vs. Non-Transplant Recipients (No)

PO0236

The Quality of Discharge Summaries After AKI

Cameron Giles, Milica Novakovic, Wilma M. Hopman, Samuel A. Silver. Queen’s University, Kingston, ON, Canada.

Background: Patients who survive acute kidney injury (AKI) are at increased risk of hospital readmission, chronic kidney disease (CKD), and death. However, most patients are unaware they experienced AKI, emphasizing the importance of high-quality communication between inpatient and outpatient health care providers. Our objectives were to determine how often different elements of AKI were mentioned in discharge summaries and to identify predictors of discharge summary quality after AKI.

Methods: We performed a retrospective chart review of 300 randomly selected discharge summaries from 2015 to 2019. We included 150 hospitalizations before and after introduction of a post-AKI clinic in August 2017, with 50 patients from each kidney Disease Improving Global Outcomes (KDIGO) AKI stage. We assessed each discharge summary for 10 elements, including AKI course and follow-up recommendations. We used multivariable logistic regression to determine predictors of discharge summary quality.

Results: The median number of AKI elements mentioned was 4/10 (IQR, 2-6). Follow-up with nephrology was documented for 33 (11%) patients. AKI-specific recommendations for labs and medication changes were noted in 66 (22%) and 80 (27%) discharge summaries, respectively. The odds of having a higher quality discharge summary (AKI elements 4/10) were greater for every increase in baseline creatinine (Cr) of 25 mmol/L (OR, 1.86; 95% CI, 1.42-2.43); intrarenal etiology (OR, 2.33; 95% CI, 1.23-4.41); increased AKI severity (stage 3 or kidney replacement therapy (KRT)) (OR, 6.85 and 4.39; 95% CI, 2.83-16.59 and 1.53-12.58, respectively); inpatient nephrology consultation (OR, 10.53; 95% CI, 8.21-22.98); and discharge Cr ≥100% above baseline (OR, 4.88; 95% CI, 1.80-13.26). Discharge summary quality did not improve with the introduction of a post-AKI clinic (OR, 0.76; 95% CI, 0.44-1.31).

Conclusions: Overall discharge summary quality in AKI survivors is poor, improving modestly for patients with baseline CKD, intrarenal etiology, severe AKI, higher discharge Cr, and inpatient nephrology involvement. Most discharge summaries are missing key post-AKI elements, including Cr trajectory and AKI-specific follow-up recommendations, even in patients receiving KRT. These gaps suggest an opportunity exists to improve discharge summary quality and communication post-AKI, especially for patients not assessed by nephrology as inpatients.
**PO0238**

Outpatient Dialysis Prescription as Predictor and Modifiable Factor for Outcomes of Patients with Dialysis-Requiring AKI

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**Background:** Patients with acute kidney injury requiring hemodialysis (AKI-D) have poor prognosis. Beginning January 1, 2017, End Stage Kidney Disease (ESKD) facilities were allowed to furnish dialysis services to AKI-D patients. Identifying modifiable predictors of AKI outcomes will allow better care of patients with AKI-D.

**Methods:** Patients with AKI-D discharged for outpatient hemodialysis (IDH) to one of 11 University of Virginia dialysis units from 1/1/2017 to 12/31/2019 (n=274) were followed for up to 6 months. Multinomial logistic regression was used to estimate association between clinical and dialysis factors and outcomes: recovery (patient off dialysis), ESKD, or death at 3 and 6 months. Dialysis data from the first 28 days were analyzed.

**Results:** Patients were 42% female, 67% Caucasian with mean age 62.8 ± 15.4 years. Comorbidities included diabetes mellitus (42%), hypertension (78%), congestive heart failure (18%), coronary artery disease (27%), prior AKI episode (36%) with pre AKI eGFR 33.8 ± 29.1 mL/min. Median (IQR) number of dialysis sessions was 11 (6-16), lasting 3.6 ± 0.6 hours. Patients declined ESKD had more median drops in blood pressure (BP) (16) than those who recovered (9) or died (10). At 90 days post start of outpatient HD, 45% recovered, 45% were declared ESKD and 9.9% died. Two more patients recovered, 2 patient died with one patient who was initially off HD was declared ESKD by 180 days. Patients with more frequent BP drops had increased odds ratio (OR) of ESKD compared to patients in the lowest quartile. Adjusted odds ratios (95% CI) for ESKD were 3.8 (1.4 – 9.7, p<0.01) and 2.1 (1.1 – 7.2, p=0.05) for patients in 3rd and 4th quartiles, respectively, adjusting for prior AKI, age, baseline cGFR, hypertension, and UF rate. The magnitude of drop in mean arterial blood pressure was not associated with ESKD or death. Net ultrafiltration (UF) (L/hts) and UF rate (ml/kg/hour) were associated with ESKD. OR (95% CI) 1.6 (1.0 – 2.5, p=0.05) and 1.2 (1.0 – 1.3, p<0.01) respectively.

**Conclusions:** Optimizing dialysis prescription and close monitoring of outpatient dialysis for patients with AKI-D is crucial and may improve outcomes of these patients.

**PO0239**

Exploratory Diagnostic and Prognostic Biomarkers in Adults with Atypical Hemolytic Uremic Syndrome (aHUS): Analysis of the Phase 3 Study of Ravulizumab (NCT02949128)

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**Background:** Validated biomarkers for diagnosis and monitoring of patients with complement-mediated thrombotic microangiopathy (CM-TMA) are not clinically available. Characterization of biomarkers in patients with aHUS, a form of CM-TMA, may inform diagnosis, treatment decisions and monitoring for patients with other types of CM-TMA.

**Methods:** Using data from the phase III study of ravulizumab (terminal C5 complement inhibitor) in adults with aHUS (NCT02949128), baseline (BL; prior to treatment) serum, plasma and urine biomarker levels in patients were compared with levels in healthy volunteers (HV), and evaluated for associations with kidney function (eGFR, proteinuria). HV, and associations between BL biomarker levels and both BL eGFR, hypertension, and UF rate. The magnitude of drop in mean arterial blood pressure was not associated with ESKD or death. Net ultrafiltration (UF) (L/hts) and UF rate (ml/kg/hour) were associated with ESKD. OR (95% CI) 1.6 (1.0 – 2.5, p=0.05) and 1.2 (1.0 – 1.3, p<0.01) respectively.

**Conclusions:** Optimizing dialysis prescription and close monitoring of outpatient dialysis for patients with AKI-D is crucial and may improve outcomes of these patients.

**PO0240**

Urineal Follistatin: A Novel Biomarker for Monitoring the Severity of AKI

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**Background:** Activin A, a member of the TGF-beta superfamily, which was absent in normal kidney, increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury. However, the role of follistatin, an endogenous antagonist of activins, in the kidney is unknown. To address this issue, we examined the localization of follistatin in normal and ischemic rat kidney, and measured urinary follistatin in both rats and humans with AKI.

**Methods:** Using vascular clamps, renal ischemia was induced for 45 min in 8-week-old male Wistar rats. Localization of follistatin in the kidney and urinary follistatin was examined by immunostaining and ELISA, respectively. Renal tissues of Nephrectomized kideny was used as normal human kidney (Approved number A18-150). Patients with AKI (n=98) and healthy adults (n=10) were enrolled in this study (Approved number A18-081 and A18-089). Serum and urinary follistatin was measured by ELISA. Correlations of urinary follistatin with other clinical parameters were analyzed.

**Results:** Follistatin was localized in renal tubules of normal rat kidney. Follistatin-expressing cells were positive for RCC and uromodulin, but were negative for AQPI or AQP2. In contrast, follistatin expression was increased in the inner medulla of the kidney after renal ischemia. Urinary follistatin, undetectable in normal rats, was significantly increased with a peak at 24 h after renal ischemia. Consistent with normal rat kidney, follistatin was localized in renal tubules of normal human kidney. Urinary follistatin, undetectable in healthy adults, was significantly increased in patients with AKI (0.0 ± 0.0 vs. 433.6 ± 428.3 pg/mL, p<0.05) and was positively correlated with the severity of AKI. Urinary follistatin was significantly increased in patients requiring renal replacement therapy compared to those who did not (911.7 ± 428.3 vs. 94.4 ± 40.0 pg/mL, p<0.05).

**Conclusions:** Follistatin, which is localized in the distal tubules of normal kidney, become detectable in the urine of AKI patients. Urinary follistatin may reflect the severity of acute tubular damage.

**PO0241**

RB1 Safety and Cytoprotective Response Biomarkers in Healthy Volunteers and Subjects with CKD

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**Background:** RB1-1 (stannous protoporphyrin [SnPP] with iron sucrose [FeS]) is a novel drug designed to precondition organs to prevent acute injury via activation of Nr2, anti-inflammatory, and iron sequestering pathways. Pretreatment with RB1-1 in several animal models of acute kidney injury (AKI) has demonstrated protection from AKI in conjunction with upregulation of cytoprotective proteins. Here, we report results of a Phase 1b study of RB1-1 that assessed safety, tolerability, and cytoprotective biomarker induction in healthy volunteers and subjects with stage 3 and 4 chronic kidney disease (CKD).

**Methods:** Fifty-four (54) subjects (18 healthy volunteers and 36 subjects with CKD) were enrolled and received a single IV dose of RB1-1 (9, 27, 45, 63, or 90 mg SnPP with 240 mg FeS). Plasma heme oxygenase-1 (HO-1), interleukin-10 (IL-10) and ferritin were selected as surrogate measures of organ protective activity. Safety was assessed through Day 29, and cytoprotective response biomarkers were assessed through 168 hours post-dose.

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**Table 1: Baseline biomarkers**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline</th>
<th>RB1 Safety</th>
<th>Cytoprotective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine copper CT</td>
<td>1.01 (0.65)</td>
<td>0.22 (0.20)</td>
<td>0.27 (0.20)</td>
</tr>
<tr>
<td>Plasma bilirubin</td>
<td>10.7 (8.20)</td>
<td>10.7 (8.20)</td>
<td>10.7 (8.20)</td>
</tr>
<tr>
<td>Plasma CRP</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
</tr>
<tr>
<td>Plasma IL-10</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
</tr>
<tr>
<td>Plasma ferritin</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
<td>0.30 (0.00)</td>
</tr>
</tbody>
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*compared with observed maximum for HV. **urine sC5b-9 is undetectable in HV, therefore HV values were set at ½LLOQ*
Ill-17 Levels Are Higher in Patients with AKI and Associate with AKI: Clinical, Outcomes, and Trials

PO0242

IL-17 Levels Are Higher in Patients with AKI and Associate with Mortality and Major Adverse Kidney Events

Jason A. Collett, Victor M. Ortiz-Soriano, Xilog Li, Alexander H. Flannery, Robert D. Toto, Orson W. Moe, David P. Basile, Javier A. Neyra, Indiana University School of Medicine, Indianapolis, IN; University of Kentucky Medical Center, Lexington, KY; The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Inflammatory markers of AKI have garnered attention for having potential to be sensitive biomarkers for AKI prognosis. We demonstrated that TH17 cells are increased in ICU patients diagnosed with AKI vs. those without AKI. The main objective of this study was to examine the association of serum IL-17 with mortality and major adverse kidney events (MAKE) in critically ill patients with and without AKI.

Methods: Multicenter prospective study of 299 critically ill patients with AKI stage 2 or above, and matched ICU patients without AKI. Blood samples were collected within 48 hours after AKI diagnosis (n=153) or within 48 hours of ICU admission in those without AKI (n=146). Serum IL-17a was measured using extremely sensitive ELISA (S-Plex technology, Mesa Scale Discovery). Logistic regression was used to examine the association of IL-17 levels with hospital mortality at 90 days post-discharge (composite of death, need of renal replacement therapy or inability to recover at least 70% of baseline eGFR). Risk of death was calculated using Kaplan-Meier survival with log-rank test. Variables included age, sex, race, APACHE II score, and serum creatinine. The association of IL-17 with mortality and MAKE was evaluated using multivariable logistic regression models, including age, sex, race, APACHE II score, serum creatinine, and serum IL-17.

Results: Patients in the highest tertile of IL-17 were more severely ill than those in lower tertiles (OR 2.33 (95% CI 1.73%-7.14%)), more frequent mechanical ventilation (63% vs. 48% vs. 44%, p=0.021), and higher APACHE-II scores (19 vs. 15.5 vs. 14, p=0.001). Moreover, patients in the highest tertile of IL-17 had higher rates of inpatient mortality (26% vs. 8% vs. 11%, p=0.002) and MAKE=90 (25% vs. 19% vs. 10%, p=0.001) and MAKE=90 (25% vs. 19% vs. 10%, p=0.001) and MAKE=90 (25% vs. 19% vs. 10%, p=0.001) and MAKE=90 (25% vs. 19% vs. 10%, p=0.001) and MAKE=90 (25% vs. 19% vs. 10%, p=0.001). In multivariable models, patients in the highest tertile (vs. lowest tertile) had increased risk of hospital mortality (aOR 2.80, 95% CI 1.09-7.20) and MAKE-90 (aOR 3.51, 95% CI 1.72-7.14). Concordant results were obtained when IL-17 was analyzed as a continuous variable.

Conclusions: Higher levels of IL-17 during acute illness are independently associated with hospital mortality and MAKE-90 in critically ill patients with and without AKI. Further studies are needed to validate the use of IL-17 as a surrogate pathobiologic and prognostic marker in this susceptible population.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO0243

Serum Renin and Major Adverse Kidney Events in Critically Ill Patients: A Multicenter Prospective Study

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Background: Preliminary studies have suggested that the renin-angiotensin system (RAS) is activated in critical illness and associated with mortality and adverse kidney outcomes. We sought to assess in a larger, multicenter study the relationship between serum renin measurements and Major Adverse Kidney Events (MAKE) in the intensive care unit (ICU) patients.

Methods: Prospective, multicenter study at two institutions of patients with and without acute kidney injury (AKI). Blood samples were collected for renin measurement a median of 2 days into the index ICU admission (T1) and 5-7 days later (T2). The primary outcome was MAKE at hospital discharge, a composite of mortality, kidney replacement therapy, or reduced estimated glomerular filtration rate to ≤ 25% of baseline.

Results: Two hundred and eighty patients were enrolled with available blood samples for 216 patients. Patients in the highest renin tertile were more severely ill overall, and serum renin was significantly higher at both time points in patients with AKI, those who experienced MAKE, and those who died (Fig. 1). In a multivariable logistic regression, this initial measurement of renin (T1) was significantly associated with MAKE. third tertile of renin, including more frequent AKI (OR 3.33 (95% CI 1.01-10.54) and severe AKI (OR 2.51 (1.08-5.80) in reference to the first tertile. Similar results were noted for renin’s association with hospital mortality. The association of renin with MAKE events in survivors was not statistically significant. The trajectory of the renin measurements between T1 and T2 was distinct when comparing death vs. survival, but not when comparing MAKE vs. those without.

Conclusions: In a broad cohort of critically ill patients, serum renin measured early in the ICU admission is associated with MAKE events at discharge, particularly mortality.

Funding: NIDDK Support, Other NIH Support - NCATS

Serum renin in patients with and without AKI, MAKE, and mortality.

PO0244

Urinary Epidermal Growth Factor and CKD Progression: The ASSESS-AKI Study

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Background: Acute kidney injury (AKI) and chronic kidney disease (CKD) are interconnected syndromes with AKI recognized as a risk factor for CKD incidence or progression. However, biomarkers of repair or resilience, such as epidermal growth factor (EGF), may help inform this risk, given the limitations of serum creatinine (sCr) in the setting of AKI.

Methods: We enrolled 1,538 hospitalized patients prospectively in the multicenter Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study. We measured urinary epidermal growth factor (uEGF) from samples at 3 months post-discharge. The primary outcome was a composite of CKD incidence, progression, or development of end-stage kidney disease (ESKD). We also evaluated change in estimated glomerular filtration rate (eGFR) over time by EGF quartile.

Results: 299 (20%) patients developed the primary outcome at a median of 4.3 years follow-up. Patients in the fourth quartile of uEGF had higher eGFR at baseline and at 3-year follow-up compared to those in quartiles 1-3, as well as significantly lower albuminuria. Each 2-fold higher uEGF level was significantly associated with decreased risk of the composite outcome (HR 0.65; 95% CI 0.59-0.71). This association remained robust after adjustment for demographic factors, baseline kidney function, urinary albumin, and other urinary biomarkers of injury and inflammation (HR 0.65; 95% CI 0.54-0.79). Patients in uEGF quartile 1 had the fastest decline in eGFR (-5.6% per year), compared to patients in uEGF quartiles 2-4 (-3.2, -2.8, -2.3% per year, respectively).

Conclusions: Urinary EGF is a marker of repair after kidney injury, and higher levels of albuminuria are associated with reduced risk of CKD and progression to ESKD in hospitalized patients with and without AKI.

Funding: NIDDK Support
Dicarbonyl L-Xylulose Reductase (DCXR) as Surrogate for “Muddy” Brown Granular Casts and Diagnostic Biomarker for Acute Tubular Injury

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Background: Detection of abundant “muddy” brown granular casts (MBGC) during microscopic examination of the urinary sediment (MicrExUrSed) is pathognomonic of acute tubular injury (ATI). Because hospital laboratories do not optimally report MBGC, nephrologists have to independently perform MicrExUrSed. Thus, a diagnostic test to identify MBGC without performance of MicrExUrSed could be clinically useful. Unlike most AKI biomarker discovery approaches, we hypothesized that MBGC-enriched urinary sediment (MBGC-sedi) contains unique proteins that could serve as biomarkers of ATI.

Methods: MicrExUrSed was performed in specimens from patients with acute kidney injury (AKI) seen for nephrology consultation with a suspected etiology of ATI. Specimens from 3 patients containing numerous MBGC (>10 per low power field in >50% of slide) were collected, subjected to low speed centrifugation (100g), proteolytically digested and analyzed by nano-LC tandem mass spectrometry. Identified proteins were quantified by normalized spectral abundance factor (NSAF). Proteins were identified by Mascot and accepted at <1% false discovery. Presence of proteins in casts was verified by immunofluorescence (IF) and western blotting (WB).

Results: A total of 242 proteins were significantly more abundant in MBGC-sedi specimens respect to the supernatant (p<0.05). Among the identified proteins unique to the MBGC-sedi, the most abundant L-xylulose reductase (DCXR) was selected as a candidate ATI biomarker because it was the protein with the lowest p value for MBGC-sedi specificity (p=0.00012, per NSAF) and only identified in MBGC-sedi. To validate the proteomics, in a separate set of MBGC-sedi specimens from patients with AKI due to ATI (n = 10), presence of DCXR was probed by WB and detected in 6 of 7 cases, and DCXR localization within MBGC by IF was verified in 3 of 3 cases.

Conclusions: DCXR is abundant in MBGC-sedi and may be a biomarker of ATI as an etiology of ATI. DCXR is an enzyme expressed in the kidney, primarily localized in proximal tubuli, and its activity is involved in carbohydrate metabolism and osmotic stress detoxification. We conclude that urinary DCXR is a potential target molecule for ATI diagnosis.

Funding: Other NIH Support - NIH R15DK124846

Preoperative Plasma TNFR1, TNFR2, and KIM-1 and Long-Term Adverse Events After Cardiac Surgery: The TRIBE-AKI Study

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Background: Plasma TNFR1, TNFR2, and KIM-1 have been associated with CKD progression in ambulatory patients with/without diabetes. However, their role as predictors of long-term outcomes and their ability to discriminate such outcomes compared to clinical parameters prior to cardiac surgery is unknown.

Methods: Prospective, multicenter cohort study of high-risk adults undergoing cardiac surgery (2007-2010). We assessed the association between pre-operative levels of TNFR1, TNFR2, and KIM-1 (natural log-transformed) and long-term mortality, CKD (incidence/progression), and cardiovascular (CV) events. We also examined the potential effect modification of DM status on the relationship between these biomarkers and outcomes. C-statistic analysis was used to quantify the discriminatory ability of the biomarker beyond the clinical model.

Results: 1378 participants (69.1% male) with a mean age: 71.9 ± 9.7, were followed for a median of 5.6 (IQR 4.3-8.6) years. 434 (31.5%) died within the study timeframe. 251 (30%) developed CKD, & 256 (19%) had CV events. After adjustment for covariates, each 1 standard deviation increase in biomarker concentration was associated with a hazard ratio (HR) of 1.16 (95% CI: 1.07-1.26) for the test set. Similar effect sizes were seen for all 3 biomarkers in their association with CV & CKD events (Figure 1).

Conclusions: Preoperative plasma TNFR1, TNFR2, and KIM-1 were independently associated with long-term outcomes after cardiac surgery and improved discrimination compared to standard clinical models. Pre-operative plasma biomarkers may serve with timely risk-stratification and planning to prevent clinical sequelae.
Results: 207 (27%) participants developed composite CKD outcome at median follow-up of 4.7 years. UCr and UOsm during hospitalization were inversely associated with developing CKD (HR 0.84, 95% CI 0.73-0.96 for UCr; HR 0.81, 95% CI 0.71-0.93 for UOsm). Figure 1 shows the hazard ratio of urine biomarkers collected during hospitalization with the composite CKD outcome using the four approaches to account for urine concentration. The association between urine kidney injury molecule-1 (KIM-1), albumin and CKD strengthened after indexing to or adjusting for UCr or UOsm, but uromodulin’s (UMOD) inverse association with CKD was blunted after indexing to UCr or UOsm.

Conclusions: UCr and UOsm, potential markers for tubular health, are both associated with lower risk of developing CKD in hospitalized AKI patients. Indexing to UCr or UOsm strengthens the biomarker-CKD associations for urine KIM-1 and albumin, but attenuates UMOD’s inverse association with CKD.

Funding: NIDDK Support

PO0249

Clinical Factors Affecting Continuous Renal Replacement Therapy Circuit Life Span
Jae seok Kim, Hanwul Shin, Kim Yoojinn, Jun Young Lee, Jae Won Yang, Byoung Geun Han, Seung-Ok Choi. Yonsei University Wonju College of Medicine, Wonju, Republic of Korea.

Background: CRRT is a useful dialysis modality in hemodynamically unstable patients. But despite use of anticoagulants, clotting of CRRT circuit frequently occurs, which reduces the efficiency of dialysis. In the study, we aim to investigate the clinical factors contributing to CRRT circuit clotting.

Methods: The medical records of total 119 critically ill patients requiring CRRT were reviewed retrospectively. We investigated the clinical factors affecting the time from CRRT start to first dialysis circuit clotting, and the proportion of dialysis circuit changes due to clotting to total circuit changes during entire CRRT periods.

Results: Un-tunneled femoral hemodialysis catheter had a shorter time to first circuit clotting (22.8 vs. 32.1 hours, p=0.013), and a higher rate of circuit clotting (52.6 %, p=0.043) than jugular catheter. The time to first circuit clotting had a negative correlation with norepinephrine dosage (r=-0.335, p=0.002) and serum creatinine level (r=-0.402, p<0.001), while it had a positive correlation with arterial blood ionized calcium (r=0.273, p=0.017). In multiple regression analysis, it was confirmed that high calcium (r= -0.460, p<0.001) and arterial blood ionized calcium (r= -0.402, p<0.001) were significant predictors contributing to CRRT circuit clotting.

Conclusions: Increased clotting events and decreased percent dose delivery were associated with the use of smaller catheters, and significant variation in average undelivered hours of CRRT per patient across units, both of which highlighted the need for shared institutional standards and more frequent measuring of adherence to those standards to improve overall CRRT delivery.

Funding: Clinical Revenue Support

PO0250

CRRT Dose Variation Across Multiple ICUs: A Single-Center Study
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1Medical University of South Carolina, Charleston, SC; 2Nara Kenritsu Ika Daigaku Fuzoku Byoin, Kashihara, Japan.

Background: Continuous Renal Replacement Therapy (CRRT) is increasingly a cornerstone of critical care provision in Intensive Care Units (ICUs) but variation in utilization and differences in culture of practice impact percentage of dose delivered, bearing on outcomes. Efforts to establish timing for initiation, modality, and type of anticoagulation continue, but standardizing local practice may be a more feasible approach to improvement, through establishing standards across units and measuring adherence to those standards.

Methods: Our study was undertaken from 02/2017 to 07/2019, and includes 150 ICU patients who received CRRT across our system’s 5 adult ICUs.

Results: We found CRRT delivery ranging from 92.7% to 96.4% of prescribed dose across our ICUs, with 12,745 hrs of CRRT delivered out of 13,575 hrs CRRT prescribed, and a weighted mean of ~7.8 hrs undelivered CRRT per patient for all patients in the study. It was lowest <60 days (p=0.001). Undelivered CRRT ranged from 3.4 hrs/patient in the Medical ICU to 13.1 hrs/patient in our Cardio Vascular ICU; the use of a smaller French catheter size for the patients on a specialty surgical ICU, and interruptions for surgical procedures, accounted for the greatest deviation from the mean for delivered CRRT; significant inter-unit variability of delivered CRRT dose per patient was also noted.

Conclusions: Increased undelivered hours of CRRT per patient across units, both of which highlighted the need for shared institutional standards and more frequent measuring of adherence to those standards to improve overall CRRT delivery.

Funding: Clinical Revenue Support

PO0251

Prediction of the Clinical Outcomes in Patients with CRRT Using Body Composition Monitoring: A Machine Learning Approach to a Multi-center Cohort Study
Kyung Don Yoo,7 Junhyug Noh,8 Jung Nam An,7 Seon Ha Baek,3 Shin Young Ahn,7 Harin Rhee,2 Eun Young Seong,3 Jae Hee Cho,1 Dong Ki Kim,1,10 Sejong Kim,3,8 Jung Pyo Lee,7,10 Yusan University Hospital, Ulsan, Republic of Korea; 2Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; 3Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 4University of Ulsan College of Medicine, Songpa-gu, Seoul, Republic of Korea; 5Harvard Medical School, Boston, MA; 6Department of Biomedical Informatics, University of Ulsan College of Medicine, Seoul, Republic of Korea; 7Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea; 8Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Gyeonggi, Republic of Korea; 9Korea University Guro Hospital, Seoul, Republic of Korea; 10Kyujeongkook National University, Daegu, Daegu, Republic of Korea; 11Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; 12Pusan National University Hospital, Busan, Republic of Korea.

Background: Fluid balance is a critical predictor of patient outcomes with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). However, accurate assessment and application of fluid balance monitoring for predicting clinical outcomes in these patients was inconclusive.

Methods: In a multicenter cohort study, a total of 784 patients with severe AKI requiring CRRT were recruited, and body composition monitoring (BCM) using bioelectrical impedance was performed on patients who started CRRT at nine tertiary hospitals in Korea from 2017 Nov to 2019 Nov. The comparison for sequential changes of total body water was performed between the survivor and non-survivor groups using mixed-effects linear regression analysis. Machine learning algorithms were used for the modeling to predict mortality.

Results: Of the 784 patients (mean age: 63.5 years), 521 (66.4%) were male. The mean APACHE II score was 29.2±10.3 in the non-survivor group and 26.5±9.0 in the survivor group. There were no significant differences in the volume status assessed by body weight and BCM at baseline. After adjusting for confounding factors, the survivor group had a marginal benefit from fluid balance in a mixed-effects linear regression (p=0.074). From a range attribute of the decision tree model for predicted mortality, plateau count was found in the first node in the late mortality group (survival duration > 60 days). Patients with survival duration under 60 days showed increased mortality, according to the SOFA score, serum sodium, bilirubin, and target clearance in a decision tree model (AUC=0.957)(Figure 1).

Conclusions: These machine learning approaches showed that conventional parameters for predicting clinical outcomes were underestimated as notable risk factors for mortality augmented by BCM in CRRT patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

129
PO0254
The Temporal Relationship Between Ultrafiltration and Mortality in Continuous Renal Replacement Therapy
Nathaniel Hocker, Sean Pickthorn, Lewis Mann, Ravanandana Venkatasubramanian, Meenakshi Sambharia, Jonathan Nizar, Benjamin R. Griffin. The University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: In acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), studies suggest that higher ultrafiltration rate (to a point) is associated with lower mortality, but fluid gain is associated with increased mortality. However, the impact of the timing of net ultrafiltration rate (NUF) on mortality is unknown. Here we evaluated whether the relationship between NUF and mortality is mediated by temporal factors.

Methods: Adults requiring CRRT at the University of Iowa from 2019-2020 were included. Patients were excluded if they survived less than 48 hours on CRRT. Cumulative fluid volume was collected at CRRT initiation and at 24, 48, and 72 hours after initiation. NUF was calculated for each day on therapy by taking the difference in cumulative volume between timepoints and dividing by patient weight. The primary outcome was in-hospital mortality. Covariates were age, gender, BMI, illness severity, CRRT days, volume at CRRT initiation, and comorbidities.

Results: A total of 200 patients met inclusion criteria. Neither NUF from CRRT initiation to 24 hours, nor NUF from 48 to 72 hours, differed significantly between survivors and non-survivors. Strikingly, however, NUF from 24 to 48 hours was strongly statistically associated (Table 1), and remained independently associated after adjustments for covariates.

Conclusions: A temporal relationship was observed between NUF and in-hospital mortality in AKI-CRRT patients. NUF from 24-48 hours was a strong predictor of mortality, but outside of this interval no association was observed. Modern fluid resuscitation strategies emphasize the importance of timing and of appropriate de-resuscitation. A similar paradigm may be advisable in CRRT, but further studies are needed.

Table 1. Net ultrafiltration rate by day in survivors and non-survivors

<table>
<thead>
<tr>
<th>Crude NUF (L/h)</th>
<th>Surviving Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1.99</td>
<td></td>
</tr>
<tr>
<td>2-4.99</td>
<td></td>
</tr>
<tr>
<td>5-9.99</td>
<td></td>
</tr>
<tr>
<td>10-19.99</td>
<td></td>
</tr>
<tr>
<td>20-39.99</td>
<td></td>
</tr>
<tr>
<td>40-99.99</td>
<td></td>
</tr>
<tr>
<td>100-200</td>
<td></td>
</tr>
<tr>
<td>&gt;200</td>
<td></td>
</tr>
</tbody>
</table>

* By convention, positive NUF means greater fluid loss, and negative NUF mean an overall fluid gain; NUF = net ultrafiltration.
Conclusions: KeGFR is higher in patients who succeed in stopping RRT and it may be an useful tool for decision-making. Supported by FAPESP.

Funding: Government Support - Non-U.S.

PO0256
Survival Comparison Between Continuous Venovenous Hemodiafiltration (CVVHDF) and Continuous Venovenous Hemofiltration (CVVH) for Septic AKI
Mun Jung,1 Yemidam Hospital, Cheonju, Republic of Korea.

Background: The mortality rate of septic acute kidney injury (AKI) remains high despite improvements in renal replacement technology. Adding dialysis to continuous veno-venous hemofiltration (CVVH) can increase survival in these patients, although hemodiafiltration leads to better clearance of inflammatory mediators in sepsis than hemodialysis. We tested whether continuous veno-venous hemodiafiltration (CVVHDF) is more effective than CVVH with the same net effluent according to body weight in intensive care unit (ICU) patients with septic AKI.

Methods: CVVHDF was performed using a Prismaflex (©Baxter International, Deerfield, IL, USA) with a blood flow rate (BFR) of 150 ml/min at a dialysate flow rate of 20 ml/kg/hour, in addition to a replacement fluid flow rate of 20 ml/kg/hour. In contrast, the replacement fluid flow rate of CVVH was 40 ml/kg/hour. The patient’s removal rate was individually adjusted by attending staff based on clinical status.

Results: In this prospective randomized pilot study, 100 patients were assigned to CVVH (n=47, M:F=23:22, age 64±15 years) or CVVHDF (n=49, M:F=30:19, age 65±11 years). Baseline characteristics including age, sex, body weight, serum creatinine, blood urea nitrogen (BUN), beta-2 microglobulin, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores did not vary between the two groups. There were no significant differences in the reduction ratios of serum creatinine, BUN, beta-2 microglobulin, APACHE II and SOFA scores between the two groups. Seven-, 28-, and 60-day survival also did not vary.

Conclusions: In conclusion, CVVH and CVVHDF led to similar clearance of waste products and survival at the same net effluent in this study. Future large-scale randomized prospective studies will be needed to confirm these results in critically ill patients with septic AKI.

Outcomes by treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Total CRRT Days</th>
<th>Total ICU Days</th>
<th>Renal recovery at hospital discharge (%)</th>
<th>Survival (%)</th>
<th>7 days</th>
<th>28 days</th>
<th>60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVH</td>
<td>5±2.9</td>
<td>15±10±3</td>
<td>35%</td>
<td>76%</td>
<td>67%</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>7±2.9</td>
<td>15±10±3</td>
<td>29%</td>
<td>76%</td>
<td>67%</td>
<td>80%</td>
<td>60%</td>
</tr>
</tbody>
</table>

CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVHF, continuous veno-venous hemofiltration; ICU, intensive care unit.

PO0257
Systematic Review of the Effects of High-Volume High-Flow (HVHF) in Pediatric Sepsis
Rupesh Raina,1,2 Ronith Chakraborthy,1,2 Siddhartha S. Singh,1,2 Nikhil Nair,1 Cleveland Clinic, Akron, OH; 2Akron Children’s Hospital, Akron, OH.

Background: Pediatric sepsis is a significant public health issue. This condition is exacerbated by the presence of excess serum creatinine and inflammatory cytokines that lead to deleterious effects upon the body. The current standard of care involves the use of continuous kidney replacement therapy to remove harmful cytokines until the body returns to homeostasis. In order to promote faster clearance and reduced stay in the ICU, high volume high flow has been posited as a potential new modality of choice. However there is a paucity of studies to fully elucidate its benefits.

Methods: A literature search was done using PubMed/Medline and Embase. Keywords used while conducting the literature search were, “hemofiltration OR haemofiltration OR hemodiafiltration” AND “high-volume”. The literature was reviewed by two independent reviewers, who independently assessed the quality of randomized controlled trials by using the Cochrane risk of bias tool for RCTs. And Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized controlled trials. Data was combined from studies with similar design.

Results: The primary endpoint of all cause mortality was found to be reduced by 40% across all of the pooled studies. For secondary endpoints, significant reductions of serum creatinine were found after 24 and 48 hours of use compared to the current standard of care. Additionally, duration of ICU stay and treatment course was found to be significantly shorter in HVHF patients than the current standard of care. Finally the rate of adverse effects were analyzed and there was no difference in the proportion of patients developing hypokalemia, hyperkalemia, hypernatremia or hyponatremia. The proportion of patients developing hyperglycemia was higher in patients undergoing HVHF whereas the proportions of patients developing bleeding was significantly less in patients undergoing HVHF. One study reported a total number of adverse events between the two groups which were significantly lesser in patients undergoing HVHF.

Conclusions: HVHF shows promise as a modality to treat pediatric patients with sepsis. In order to confirm the benefits of this modality, future studies need significantly more patients for analysis.

PO0258
AKI and Hospital-Acquired Sepsis in Critically Ill Children: A Retrospective Single-Center Study
Cassandra L. Formeck,1,2 Robert Feldman,1 John A. Kellum,1,2 John A. Kellum.1,2 University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA.

Background: Acute kidney injury (AKI) is common among critically ill children and is associated with an increased risk for de novo infection, however little is known about the temporal relationship between AKI and risk for subsequent infection. The objective of this study was to describe the risk of developing hospital-acquired sepsis over time following AKI onset.

Methods: We conducted a single-center retrospective cohort study of critically ill children admitted to the pediatric and cardiac ICUs at a tertiary pediatric care center in the United States. The cohort included children, ages birth to 18 years, without a diagnosis of chronic kidney disease, primary immunodeficiency, or sepsis within the first 48 hours of hospital admission. The relationship between the primary exposure (AKI) and primary outcome (development of hospital-acquired sepsis) was assessed using Cox proportional-hazards models using AKI as a time-varying covariate.

Results: Among the 5695 children included in the study, hospital-acquired sepsis was more common in the 1153 children that developed AKI (n=117, 10.7%) than in the 4542 children that did not develop AKI (n=210, 4.6%). Over a median follow-up of 3.1 days, the development of AKI was associated with an increased risk for development of hospital-acquired sepsis with an adjusted HR of 1.41 (95% CI 1.11-1.80, p=0.005). The median time from AKI onset to sepsis was 2.6 days (IQR 1.5 – 4.7). Among the 117 children who developed hospital-acquired sepsis following AKI (from 48 hours after hospital admission through hospital discharge or 30 days), 80.3% of children developed sepsis within 7 days and 96.6% within 14 days of AKI onset.

Conclusions: AKI is an independent risk factor for de novo infection. Children with AKI are at highest risk for developing hospital-acquired sepsis within 14 days following AKI onset.
PO0259
Disseminated Intravascular Coagulation Is Associated with AKI in Pediatric Severe Sepsis
Ayse Akcan Arıkan,1,2 Michael P. Smaglick,1 Vinod Vijayan,1 Curtis E. Kennedy,2 Brady S. Moffett,1 Poyyapakkam Srivaths,1 Trung C. Nguyen,1 Baylor College of Medicine, Houston, TX; 2Texas Children’s Hospital, Houston, TX; 3University of Pittsburgh, Pittsburgh, PA.

Background: Exact mechanism of pediatric septic acute kidney injury (AKI) remains unknown. Coagulation perturbations like disseminated intravascular coagulation (DIC) are frequent in sepsis and associated with organ dysfunction. The link between DIC and septic AKI has not been adequately explored in pediatric patients.

Methods: Single center cohort study of pediatric patients with severe sepsis Jan 2017-Apr 2018. Primary outcome was AKI (per Kidney Disease Improving Global Outcomes creatinine criteria), primary exposure was DIC (per International Society of Thrombosis and Haemostasis criteria).

Results: 287 patients were enrolled, median age 7.3 (IQR 1.6-14.5) years; 58% had AKI, 34% had DIC. Pediatric risk of mortality score was 8 (IQR 4-13); 57% were mechanically ventilated and 67% were on vasopressors. DIC prevalence was 52% in AKI pts vs 19% in no AKI pts (p<0.001). DIC score was higher in AKI (4.27 (IQR 3.85-4.67) vs 2.25 (IQR 1.92-2.58) in no AKI (p<0.001)). In adjusted analysis controlling for severity of illness, mechanical ventilation, and vasopressor use, DIC presence (aOR 2.6 (95%CI 1.45-4.67)) and DIC score (aOR 1.33 (95% CI 1.17-1.51)) were both independently associated with AKI.

Conclusions: DIC is very common in pediatric septic AKI. Severity and presence of DIC are both independently associated with septic AKI. Mechanistic contribution of coagulation perturbations to septic AKI and identification of potential modifiable factors require further study.

PO0260
Midterm Renal Outcomes and Renal Recovery in Pediatric Continuous Renal Replacement Therapy
Sanmer Thadani,1 Dana Y. Fuhrman,1 Claire Hanson,1 Joseph A. Carcillo,3 Poyyapakkam Srivaths,1 Ayse Akcan Arıkan,1,2 Baylor College of Medicine, Houston, TX; 2Texas Children’s Hospital, Houston, TX; 3University of Pittsburgh, Pittsburgh, PA.

Background: Most pediatric continuous renal replacement therapy(CRRT) outcomes studies focus on crude mortality. Recent data highlighted incomplete recovery and dialysis dependency in pediatric acute kidney injury treated with dialysis. We described midterm outcomes and renal recovery in pediatric CRRT.

Methods: Multicenter cohort study between 2/14-2/20. Primary outcome was Major Adverse Kidney Events at 90 days(MAKE90), secondary outcome was renal recovery (n=MAKE90 in survivors).

Results: 419 patients received CRRT for 9 days(IQR3-21) (age 93 mo (17-180), 51% male). PELOD2 was 9(7-14), 55% were ventilated, 67% were on vasoactives. 276(66%) patients had MAKE90 (61% dead, 21% dialysis dependent, 18% persistent renal failure). PELOD2 was 9(7-14), 55% were ventilated, 67% were on vasoactives. 276(66%) patients had MAKE90 (61% dead, 21% dialysis dependent, 18% persistent renal failure). Urine output at CRRT start was an independent predictor of renal recovery while admissions for metabolic/endocrine reasons are more likely to survive with intact renal function. Urine output at CRRT start is an independent predictor of renal recovery among pediatric CRRT survivors.

PO0261
AKI and Mortality in Patients Prescribed Immune Checkpoint Inhibitor Therapy
Megan L. Baker,1 Yu Yamamoto,1 Mark A. Perazella,1 Chirag R. Parikh,2 Francis P. Wilson,1 Dennis G. Moledina,1 Yale University Department of Internal Medicine, New Haven, CT; 2Johns Hopkins Medicine, Baltimore, MD.

Background: In patients on immune checkpoint inhibitor (ICI) therapy, acute kidney injury (AKI) is relatively common, and can occur from tubular injury or pre-renal azotemia unrelated to ICI use, or from off-target immune activation resulting in acute interstitial nephritis (AIN). The association of AKI and its specific etiologies with mortality is not known.

Methods: In patients initiated on ICI between 2013-2019, we tested the association of serum creatinine-based AKI with mortality up to 1 year after therapy initiation using Cox proportional hazard models controlling for demographics, comorbidities, cancer type, severity, therapy, and baseline laboratory values. In patients with AKI, we tested the association of AKI severity, AKI duration, and, using a validated risk score, AIN risk with mortality.

Results: Of 2,207 patients initiated on ICI therapy, 549 (25%) developed AKI. Mortality rate was higher in those who developed AKI (905 vs. 445 per 1000 person-years). AKI was independently associated with higher mortality [adjusted HR 2.18 (95% CI 1.38-3.45)] and this hazard was highest in the first month after AKI [9.7 (7.8-12.1)] and progressively diminished to the background rate by four months. Among patients with AKI, mortality was higher in those with severe AKI [2.03 (1.01-4.11)] and longer duration AKI [2.58 (1.01-6.60)]; but lower in those with the highest likelihood of AIN [adjusted HR highest vs. lowest tertile, 0.07 (0.02-0.29)].

Conclusions: We noted that occurrence of AKI was independently associated with higher mortality in patients treated with ICI. Among patients with AKI, mortality was higher in those with severe AKI and longer duration AKI, but lower in those with features suggestive of AIN.

Funding: Other NIH Support - R01DK113191, R01DK128087, P30DK079310, and KL2DK117065

PO0262
Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of AKI in Older Adults With Type 2 Diabetes
Min Zhuo,1,2 Julie M. Paik,2,3 Deborah J. Wexler,4 Joseph V. Bonventre,2 Seoyoung C. Kim,2 Elisabetta Patorno,1 Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital Department of Medicine, Boston, MA; 3VA New England Geriatric Research Education and Clinical Center, Boston, MA; 4VA New England Center for Clinical Research and Training, Boston, MA; 5Massachusetts General Hospital, Boston, MA.

Background: We compared the association of AKI with the initiation of a sodium-glucose cotransporter-2 inhibitors (SGLT-2i) to the initiation of a dipeptidyl peptidase 4 inhibitor (DPP-4i) or a glucagon-like peptide 1 receptor agonist (GLP-1RA) in adults aged ≥ 66 years with type 2 diabetes (T2D).

Methods: In this nationwide cohort study, we used Medicare fee-for-service from 2013 to 2017 to identify older adults with T2D. SGLT-2i initiators were 1:1 propensity score (PS)-matched to DPP-4i or GLP-1RA initiators, in two pairwise comparisons. More than 100 variables were used in the PS model, including demographic characteristics, comorbid conditions, medication use, and health care utilization. The primary outcome was a hospital discharge diagnosis of AKI in the primary or secondary position. Cox proportional hazards regression models were used to generate hazard ratios (HRs) in PS-matched groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0263
Urine Sediment Examination: Comparison Between Laboratory-Performed vs. Nephristologist-Performed Microscopy


Background: Urinalysis is a commonly performed diagnostic test in clinical laboratories and automated urine technology is becoming the standard for providing urinalysis data to clinicians. Time constraints, and automated technology reporting has resulted in a decline in clinicians performing their own urine sediment exam. We hereby look at the diagnostic accuracy of sediment suggested diagnoses in predicting the respective pathologic diagnoses.

Methods: Using our Electronic Medical Records, we identified 33 adult patients with acute kidney injury with documented nephristologist performed urine microscopy and a kidney biopsy within one week of the sediment analysis. We performed chart review to document suggested diagnoses based on urine sediment analysis and compared it to the respective pathologic diagnoses identified on the subsequent kidney biopsy. We categorized the sediment findings into four categories: bland, suggestive of acute tubular injury (sATI), suggestive of glomerulonephritis (sGN), and suggestive of acute interstitial nephritis (sAIN). Pathologic findings were categorized into ATI, GN, and AIN.

Results: The cohort demographics consisted of 18 (54.6%) male patients, 23 whites (69.7%), and a mean age of 56.6 years. Sediment analyses were bland in 6 patients (8.45%) with 5 (15.15%) sATI, 22 (66.67%) sGN, and no sAIN cases. All cases with sATI on sediment analysis showed ATI on the kidney biopsy. Similarly, all 22 cases with sGN on the sediment had a pathologic diagnosis consistent with GN on the biopsy. Of the 6 patients with bland sediment analyses, 3 showed ATN pathologically while the other 3 had GN on the kidney biopsy.

Conclusions: Urine sediment examination remains an important test than can provide important information about kidney disease. Our data shows 100% agreement between sediment analyses suggestive of ATI or GN and the pathologic diagnoses. This is important in patients in whom a kidney biopsy might be contraindicated precluding the luxury of a pathologic diagnosis. While a suggestive sediment analysis seems to carry a high predictive value, the negative predictive value of a bland sediment was low however. Overall, we believe urine sediment analysis is an important skill for the nephristologist with important patient care implications.

PO0265
Histopathological Confirmation of Acute Tubular Injury in Patients with “Muddy Brown” Granular Casts in the Urinary Sediment

Vinip Varghese, Akanksh Ramanand, Juan Carlos Velez. Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Microscopic examination of the urinary sediment (MicrExUrSed) can be a useful tool in the differentiation of acute kidney injury etiology. In particular, “muddy brown” granular casts (MBGC) are thought to be pathognomonic for acute tubular injury (ATI). However, the ability of MBGC to predict biopsy-proven ATI has not been formally examined. Thus, we hypothesized that the identification of MBGC by MicrExUrSed can accurately predict a histopathological diagnosis of ATI.

Methods: In a single-center prospective study, we selected cases of patients seen in nephrology consultation who had a urine specimen subjected to MicrExUrSed as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed within 2 weeks of the MicrExUrSed. Presence of MBGC in those cases was determined. We assessed the performance of identification of MBGC for the diagnosis of biopsy-proven ATI. Sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) of MBGC to diagnose ATI were determined.

Results: Among 371 patients in whom MicrExUrSed was completed, 49 underwent kidney biopsy and were included. Mean age was 61 years, 38% were women. White race accounted for 59% and black race accounted for 33%. Mean serum creatinine was 1.4 mg/dL. Biopsy diagnosis was ATI in 36 (73%) and non-ATI in 13 (27%). Among the 36 cases of biopsy-proven ATI, concomitant glomerular pathology was present in 19 (53%). The sensitivity of MBGC for biopsy-proven ATI diagnosis was 78% (95% CI 61-90%), while the specificity was 100% (95% CI 75-100%). The PPV of MBGC for ATI diagnosis was 100% (95% CI 100%) and the NPV was 62% (95% CI 47-93%).

Conclusions: Our data demonstrate that MBGC on MicrExUrSed are pathognomonic for ATI confirmed by kidney biopsy – with high PPV and specificity of 100%. While MBGC reflect ATI, concomitant glomerular pathology can be present in patients with MBGC in the urinary sediment.

PO0266
Feasibility of Point-of-Care Solid Organ Doppler for Assessing Emergency Department Patients with AKI

Forrest F. Lindsay-McGinn, Christy Moore, Jeffrey A. Kramer, Nova Panebianco, Felice Teran, Nathaniel C. Reisinger. University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Acute kidney injury (AKI) in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) can assist with volume assessment, which is critical to diagnose the underlying cause of AKI. We describe clinical and ultrasonographic characteristics of patients with AKI using a
POCUS protocol that examines hepatic, portal and interlobar renal vein spectral Doppler assessment previously described as the Venous Excess Ultrasound (VExUS) protocol which was found to predict AKI after cardiac surgery.

Methods: This is a prospective convenience sample of adult patients presenting to an academic, urban emergency department found to have AKI from September 2020 to May 2021, who received a POCUS examination and interpreted by an US fellowship trained emergency medicine physician under the guidance of a certified vascular US technician. Spectral Doppler assessment of hepatic, portal, and interlobar renal veins were obtained. Hepatic vein Dopplers were considered abnormal if the D wave was greater than the S wave. Portal vein Dopplers were considered abnormal if the pulsatility index was greater than 30%. Interlobar renal vein Dopplers were considered abnormal if there was phasisity. The diagnosis of AKI was established by Kidney Disease Improving Global Outcomes criteria. The institutional review board approved this study.

Results: Thirty-seven patients were included. Median age was 63 and average BMI 29. 15 experienced stage 1 AKI, 5 had stage 2 AKI, 17 had stage 3 AKI. 7 required dialysis. 70% experienced stage 1 AKI, 5 had stage 2 AKI, 17 had stage 3 AKI. Seventy required dialysis during their admission. Two were found to have an inferior vena cava (IVC). 15 had an IVC >15mm with less than 50% respiratory collapse. Of the 15 patients with plethoric IVC assessments, 11 had interpretable hepatic vein Dopplers, 4 were abnormal. 14 had interpretable portal vein Dopplers and 7 were abnormal. All had interpretable renal vein Dopplers. 18 were abnormal. The most common reasons for uninterpretable Dopplers were difficulty holding expirations, arrhythmias and liver cirrhosis or masses.

Conclusions: Our study describes the feasibility of a POCUS assessment using solid organ spectral Doppler for emergency department patients with AKI. Further research is required to understand the test characteristics solid organ spectral Doppler for assessment of this population.

PO0267
Utility of a Point-of-Care Ultrasound Volume Assessment for Emergency Department Patients with AKI: A Pilot Study
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Background: Acute kidney injury (AKI) identified in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) for AKI is recommended due to obstructive uropathy but does not routinely include volume assessment, which may be informative regarding the underlying cause of AKI. POCUS evaluation of heart and lungs has proven to be useful in assessing intravascular volume status in patients on dialysis and with heart failure. This study aims to describe the clinical and ultrasonographic characteristics of patients with AKI using a POCUS volume assessment.

Methods: This is a prospective convenience sample of adult patients presenting to an academic, urban ED found to have AKI from September 2020 to May 2021. Ultrasound was performed using an ultrasound machine with a high-end linear probe with a 5 MHz, 6 MHz and 8 MHz transducer. The diagnosis of AKI was established by Kidney Disease Improving Global Outcomes criteria. US images were obtained and interpreted by an US fellowship trained emergency medicine physician. The institutional review board approved this study.

Results: Thirty-seven patients were included. 22 were African American and 20 were male. Median age was 63 and average BMI was 29. Eight had documented CKD, 15 had diabetes, 24 had hypertension and 13 had heart failure. Prior to ultrasound assessment, 24 patients were assessed as hypovolemic, 4 as euvolemic, and 9 as hypervolemic by the ultrasound. Patients experienced stage 1 AKI, 5 had stage 2 AKI, and 17 had stage 3 AKI. Seven required dialysis during their admission. Two were found to have a bladder outlet obstruction and 4 were found to have bilateral, moderate to severe hydronephrosis. Thirty-seven had a left ventricular ejection fraction (LVEF) assessment, 21 had a right ventricular ejection fraction (RVEF) assessment, 21 had a left ventricular EF ≥55%, 10 had a right ventricular EF ≥35%, 6 had a LVEF <30%, and 9 had a right ventricular EF <30%. Thirteen had pulmonary artery B-lines suggestive of pulmonary edema. Thirty-six had an assessment of their inferior vena cava (IVC) and 15 had an IVC >15mm with less than 50% respiratory collapse.

Conclusions: Our study describes the findings of a POCUS volume assessment of ED patients with AKI. Abnormal cardiac and lung findings were common and may be a useful adjunct to IVC, kidney and bladder assessment alone.

PO0268
Addition of High-Dose Furosemide to Norephinephrine During Treatment of Hepatorenal Syndrome Type 1 Augments Diuresis and Does Not Halt Kidney Function Recovery
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Background: Withdrawal of diuretics is recommended as a first intervention in patients with cirrhosis who present with acute kidney injury (AKI) to eliminate prerenal causes of kidney injury. The use of diuretics is safe and effective.

Methods: We search records of patients hospitalized at Ochsner Medical Center over a 3 year period who received intravenous (IV) furosemide (FURO) while receiving IV norephinephrine (NE) as a vasopressor specifically for treatment of AKI due to HRS-1. We assessed the change in urine output (UOP) and the trajectory of serum creatinine (sCr) values before and after the initiation of NE and before and after the addition of FURO.

Results: A total of 19 patients with HRS-1 received IV FURO [median duration: 2 days, variability: median dose: 160-260 mg boluses q6-24 h] added to IV NE during the study period. Median age was 52 (31-69) years; 89% white race, 53% women, median MELD score 32 (22-41). At the time of initiation of FURO, median sCr was 3.8 (1.7-7.9) mg/dL. Before initiation of any therapy, the median UOP was 275 (10-695) mL/day. NE was started with a median INR of 200-213 days (p=0.013). Addition of FURO to NE induced a subsequent increase in median UOP to 2045 mL/day (p<0.001), i.e., median gain in UOP of 1605 mL/day. Fifteen (79%) patients treated with NE+FURO [median MAP rise 15 (11-24) mmHg] either maintained or improved the sCr trajectory after adding FURO (figure). The magnitude of NE-induced rise in sCr significantly correlated with the average UOP achieved during the days of combined NE+FURO therapy (R=0.48, p<0.03).

Conclusions: In patients with HRS-1 who are adequately treated with NE and achieved an optimal MAP increment, addition of high-dose IV FURO enhances diuresis without negatively affecting recovery of kidney function.
Conclusions: Among patients with HF/EF admitted for HF, achievement of faster rates of decongestion is associated with reduced risk of CVD mortality and HF hospitalization. Whether this suggests that either more rapid decongestion provides cardiovascular benefit, or whether the ability to rapidly decongest is a proxy for a healthier individual, remains to be further evaluated.

Results: (1) to develop a centralized portal that provides a living resource for the research community and access to open data sources; (2) to lower entry barriers for researchers interested in AKI by developing interactive educational content; (3) to articulate a preclinical roadmap that facilitates the development of novel interventions; and (5) to enhance communication around AKI innovation by fostering an open and vibrant community of patients, researchers, clinicians, and other stakeholders.

Conclusions: State-of-the-art medical care of AKI patients remains reactive and supportive. No targeted treatment for sepsis has been identified to prevent this syndrome or hasten the recovery to health. Lowering barriers for new entrants and increasing opportunities for collaborations across a wide spectrum of stakeholders may help promote a culture of innovation to impact AKI.

PO0273
Tele nephrology (TN) vs. Face-to-Face (F2F) Visits: A Comparison of Inpatient Nephrology Outcomes and Provider Perspectives
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Background: Clinical outcomes, patient, and provider perspectives on inpatient synchronous tele nephrology care remain largely unstudied. In this retrospective study, we compared outcomes in patients who received inpatient synchronous TN plus F2F (controls) versus only F2F (controls) at two Mayo Clinic Health System (MCHS) community hospitals.

Methods: Hospitalized adults who had nephrology consultations during 3/1/2020 to 2/28/2020 were classified in separate diagnosis groups. Logistic regression was used to assess 30-day mortality, readmissions, and hospital transfers. Penalized regression was used in the case of rare events. Negative binomial regression was fit to account for overdispersion in length of hospital stay data. Unadjusted and Adjusted odds ratio with 95% confidence intervals were calculated.

Results: A total of 850 patients were included. Mean age was 69 years, 59% were male and 93% white. Cases were more likely to get dialysis after a TN consult; OR: 1.80 (1.00, 3.22). Other outcomes were not statistically different (Table 1). Both non- nephrology hospital providers and tele-nephrologists reported the most frequent reasons for consultations were AKI, ESRD, electrolytes, or acidosis. Tele-nephrologists preferred video consultations (82%) to phone for communication. More than half (64%) of tele-nephrologists felt less stress on TN compared to F2F consults. Non-nephrology hospital providers were very satisfied 10 (48%) and satisfied 6 (29%) with TN response time, and most felt TN was as safe as F2F (67%) and provided them enough information to make patient care decisions (76%).

Conclusions: Outcomes for in-hospital nephrology consultations were similar between tele nephrology plus face-to-face and face-to-face. Non-nephrology hospital providers and tele-nephrologists had favorable opinions for TN and most thought it is as safe as F2F consults.

PO0274
Renal Cytosolic Phospholipase A2 Mediates AKI in Humans
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Background: Cytosolic phospholipase A2 (cPLA2) is a key mediator that regulates PGE2 production. PGE2 is a key mediator in the cardiovascular system.

Methods: Using a mouse model of hemorrhagic shock, we studied the role of cPLA2 in AKI. We observed that cPLA2 knockout mice had reduced AKI compared to wild-type mice. We also observed that cPLA2 knockout mice had reduced PGE2 production.

Results: In humans, we observed that cPLA2 expression was increased in patients with AKI compared to healthy controls. We also observed that PGE2 production was increased in patients with AKI compared to healthy controls.

Conclusions: Cytosolic phospholipase A2 (cPLA2) is a key mediator that regulates PGE2 production. PGE2 is a key mediator in the cardiovascular system. cPLA2 knockout mice have reduced AKI and reduced PGE2 production.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Kidneys with or without AKI were collected from deceased human transplant donors (n=10 donors; kidneys from 7 donors and AKI: 12 kidneys from 8 donors). We used LC-MS and mass-spectrometry imaging (MSI) to investigate the abundance of relevant metabolites, RT-PCR and Western blotting were used to examine the levels of lipid enzymes and PGE2 levels were investigated by ELISA. To determine whether cPLA2-PGE2 pathway mediates AKI, we stimulated RPTEC and human kidney organ culture using interleukin-1ß (IL-1ß) and cPLA2 inhibitor and investigated changes in kidney injury markers.

Results: To validate this human model of AKI, kidney injury (KIM-1 and NGAL) and cytokine (IL-6, IL-8) markers were significantly higher in kidneys collected from donors with AKI compared to kidneys collected from donors without AKI. Lipidomics showed significantly lower levels of phosphatidylcholine (PC) species (PC 29:1, 31:1, 32:4 and 35:5) and MSI showed significantly higher abundance of arachidonic acid and prostaglandins in kidneys from donors with AKI. Kidneys from donors with AKI demonstrated significant upregulation of cPLA2 mRNA and protein, and higher levels of PGE2, compared to kidneys without AKI. cPLA2 inhibitor significantly reduced PGE2 and kidney injury markers in IL-1ß-stimulated RPTEC and human kidney organ culture model.

Conclusions: Lipidomics, MSI and molecular data identify changes in the PC-cPLA2-PGE2 pathway in human kidneys obtained from AKI donors. The inhibition of cPLA2 ameliorates kidney injury in vitro suggesting that this enzyme is a key driver of AKI in human kidneys.

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PO0275
Quantitative Proteomics Analysis Identifies Novel Markers of AKI, CKD, and AKI-to-CKD transition in Human Kidneys
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Background: The etiology of AKI is multifactorial and is associated with in-hospital mortality and progression to CKD. Molecular phenotypes that are shared across AKI, CKD and the transition are unclear but may characterize common injury mechanisms that can be targeted for kidney preservation. We hypothesize that molecular interrogation of the kidney tubulointerstitial (TI) will identify proteomic signatures that reflect AKI, CKD to transition and CKD progression.

Methods: Frozen kidney biopsies from 4 CKD and 3 AKI patients obtained from procurement sites in the Kidney Precision Medicine Project were used for this study and compared to nephrectomy controls (n=4). TI was isolated using laser microdissection and recovered proteins were submitted for HPLC MS/MS proteomics analysis using Orbitrap eclipse mass spectrometer. Label-free quantification and global normalization of spectral count data was performed to determine changes in protein expression.

Results: In TIs from demonstrating kidney injury (AKI), we observed increased cell proliferation and migration (MAP1B, PPFIBP1, RASAL1, NT5C2, PTPPM1, S100A4, XRNI, MND4, SRM, MAMD2) and extracellular matrix regulatory proteins (VCAN, POSTN, TNC, PDGFB, THBS2, FBLN5, COL1A1) were upregulated in AKI while cell-cell adhesion and extracellular matrix molecules (COL1A1, POSTN, FN1, LAMA2, VCAN, FIBRIN, AIBG, MRC1, CP, STAB1, TIMP3, ITIH4, MAF4, TNC), cell proliferation (MAP1B, PTPRC, NIBAN1, FUBP1, S100A4, PPFIBP1, ARHGGD) and inflammation markers (C2, SAMHD1, IL16, C7) were upregulated in CKD compared to controls. Overall, 57% and 28% of up- and downregulated proteins in AKI, were shared in CKD and may reflect AKI to CKD transition.

Conclusions: Proteomic analysis of the TI identified known and novel markers specific to AKI and CKD. Additionally, activation of common inflammatory and extracellular matrix remodeling proteins in AKI and CKD settings suggests that unified pathways activated in the TI could underlie AKI to CKD progression. The causal role of these candidate markers in the pathogenesis of AKI and CKD needs to be better defined, but if validated, targeting these pathways could help arrest tissue injury and limit disease progression. This work is ongoing.

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PO0276
Leishmania infantum-Induced Acute on Chronic Interstitial Nephritis
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Introduction: Leishmania is an exceedingly rare yet important cause of acute and chronic interstitial nephritis (CIN) that can lead to severe renal dysfunction, necessitating dialysis if unaddressed.

Case Description: A 53-year-old man presented with a progressive rash, cyclic hypercalcemia, and 24-hour urine creatinine of 2 g/day, 1 year, and previously had traveled to South Africa and Africa multiple times. Due to compressive symptoms and pancreatitis, the patient underwent splenectomy and lymph node biopsy which yielded Leishmania infantum (Figure 1A). In our institution, he was oliguric and hypertensive. Labs showed Na 129, K 5.3, HCO 8.8, BUN 144, Cr 12.6 mg/dL (baseline Cr 0.8 last year), and elevated LFTs. UA showed ATN casts. 24-hour urine protein was 1.8 grams. SLEP/UPPEK and K/L ratio were normal. Due to concerns for AIN, CIN, infectious GN vs. amyloidosis, a kidney biopsy was pursued after HD initiation. Biopsy revealed chronic active tubulointerstitial nephritis associated with marked interstitial plasma cell infiltrate and moderate fibrosis without evidence of glomerular disease (Figure 1B). Amphotericin B was started. Steroids were not initiated given moderate fibrosis and risk for blunting response against Leishmania. His rash and LFTs improved rapidly yet, he required HD 3 times a week at discharge. 9 weeks after amphotericin initiation, his HD requirement is now reduced to twice weekly and pre-HD creatinine levels continue to decrease.

Discussion: Leishmaniasis is a rare cause of kidney injury in the US. CIN is the most common underlying pathology in these patients. A high index of suspicion in the appropriate clinical context is necessary to institute timely interventions to prevent long-term sequelae. Patients with visceral leishmania and kidney dysfunction should be evaluated for interstitial nephritis as a potential cause when alternative etiologies have been ruled out.

PO0277
Too Much of a Good Thing: A Case Report of Suspected Acute Tubular Necrosis Potentiated by Hypervitaminosis D
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Introduction: While Vitamin D deficiency is prevalent in the United States, vitamin D toxicity remains a rare pathology. More novel is the incidence of acute kidney injury facilitated by calcitriol toxicity, with a PubMed search yielding less than twenty results, a majority of which come from foreign journals. Tubular injury propagated by calcitriol has been demonstrated both in vivo, and from biopsies in even fewer case reports.

Case Description: A middle age man presented to the ED after routine labs demonstrated an acute kidney injury approximately four times his baseline creatinine, with mildly elevated hypercalcemia. Creatinine was within normal limits 1 year prior. Workup for his hypercalcemia revealed a markedly elevated 25 vitamin D >480, exceeding the quantifiable limit of the lab equipment. The patient reported a two week history of vitamin D supplementation of approximately 210,000 IU daily. Even with stabilization of his hypercalcemia, fluid resuscitation and cessation of his supplements, the patient did not recover his baseline kidney function at discharge, nor at follow-up three months later. The patient had no medical history predisposing him to chronic kidney disease, with labs non-contributory for any other nephritic or nephrotic process, but suggesting an intrinsic, tubular pathology. With other etiologies essentially ruled out, in the setting of recent consumption of massive amounts of Vitamin D, the diagnosis of ATN secondary to hypervitaminosis D was suspected.

Discussion: Hypercalcemic AKI, at calcium levels as high as 19.9 mg/dL, typically resolves with treatment within 1-2 weeks; this patient failed to resolve, suggesting an additional insult. In calcitriol-induced AKI, toxicity of excess free Vitamin D metabolites exceeds the capacity of neutralizing vitamin D binding proteins. In vitro, calcitriol potentiates ATP depletion, and cytotoxicity of renal tubular cells even in the absence of hypercalcemia. In vivo, excess calcitriol exacerbates cellular autolysis by 2-3 times even with only modest hypercalcemia. Similar case reports describe biopsy evidence of tubular injury caused by vitamin D toxicity, with recovery of baseline creatinine taking between 3 months to 2 years. As incidence of vitamin intoxication increases, vigilance toward the harms of these supplements are important to recognize in healthy patients presenting with AKI.
AKI: Trainee Case Reports

PO0280

A Nutty Case of Oxalate Nephropathy

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Introduction: Oxalate nephropathy occurs when considerable amounts of calcium oxalate crystals deposit in the renal parenchyma. Excessive dietary intake of oxalate-rich foods (including some associated with healthy eating) in otherwise healthy individuals can lead to secondary oxalate nephropathy. We report a case of severe AKI related to excessive nut consumption.

Case Description: A 41-year-old man with history of Hashimoto’s disease and pancytopenia presented to the hospital with 1 week of nausea and vomiting. Evaluation showed AKI with elevated serum creatinine (19.9 mg/dL), BUN (229 mg/dL), hematuria, and proteinuria (urine protein/creatinine ratio 1.6 gm/gm). Serologic workup showed mildly elevated kappa/lambda ratio (3.52) and low C3 (71mg/dL) but was otherwise unremarkable. Serum uric acid was high at 11.6 mg/dL. Renal ultrasound revealed normal kidney size with increased parenchymal echogenicity and punctate echogenic foci bilaterally. A renal biopsy was performed demonstrating widespread oxalate deposition with associated interstitial inflammation and tubular injury. Further history revealed no recent medications, infections, or ingestions, but did uncover a high intake of nuts (~1 pound) daily over the prior 1 year due to their perceived health benefits. He remained hemodialysis dependent on hospital discharge.

Discussion: Secondary oxalate nephropathy can result from increased enteric oxalate availability from dietary consumption. Diagnosis can be delayed when a review of diet and supplements is deferred. It is therefore essential to obtain a detailed dietary and pharmacologic history, particularly in all patients with unexplained kidney disease. Treatment is supportive including decreasing the high oxalate culprit foods in the diet.

PO0281

Case Report of Rivaroxaban-Induced Anticoagulant-Related Nephropathy

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Introduction: Anticoagulant related nephropathy (ARN) is still an under recognized etiology of acute kidney injury (AKI). There are no guidelines for ARN treatment to date and the literature consists mostly of case reports. While early detection of AKI remains the most important treatment, discontinuing the offending agent and antidote administration are also crucial. Other measures utilized include administering fluids and urine alkalization to minimize red cell precipitation.

Case Description: Our patient is a 63-year-old Hispanic male treated with Rivaroxaban for atrial fibrillation. He started experiencing increased hemorhaging with progressive worsening kidney function over two months. His serum creatinine (sCr) increased to 3.35mg/dL from 0.83mg/dL. Initial work up only revealed hematuria on a urinalysis. Serologies including auto-immune and hepatitis panels were negative. Subsequently, a renal biopsy done revealed chronic IgA nephropathy and acute tubular injury with prominent RBC casts and intratubular red blood cells. This was suggestive of ARN in the absence of glomerular dysfunction. The causative agent was held and a bicarbonate infusion was initiated. The patient’s renal function improved with a most recent sCr of 1.5mg/dL consistent with an estimated glomerular filtration rate (eGFR) of 50 ml/min/1.73m2 improved from 19, approximately 7 months after initial treatment.

Discussion: Our case provides another example of ARN and highlights the therapeutic measures utilized. ARN has previously been shown to hasten CKD progression with increased mortality. Early identification and therapeutic management can lead to considerable renal recovery as seen in our patient’s case. More studies are needed to further clarify the pathophysiology of ARN and to investigate potential treatments.

PO0279

AKI Associated with Hydrophilic Polymer Embolism: A Case Report

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Introduction: Minimally invasive endovascular procedures have become increasingly popular. Technology has improved, allowing the use of hydrophilic polymers to coat surgical tools such as catheters, guidewires, and sheaths to reduce vasospasm and trauma to vessels. However, a complication of using hydrophilic polymers is embolization of the material to distal small arteries, causing ischemia of organs such as the lung, brain and kidneys. Although hydrophilic polymer embolization has recently increased in recognition, only a few cases of renal embolization have been reported.

Case Description: Here we present the case of a 73-year-old male with history of peripheral artery disease and no previous diagnosis of kidney disease who was admitted to the hospital due to acute oliguric acute kidney injury (AKI), four weeks after undergoing an endovascular aneurysm repair with aorto-uni-iliac stent, right femoral endarterectomy and right femoral-popliteal bypass. Laboratory work-up such as complement levels, viral and antibody serologic testing were unremarkable. His hospital course was complicated by anuria, hyperkalemia and hyperphosphatemia. Kidney biopsy (figure 1) showed a foreign material consistent with a hydrophilic polymer embolism, as well as histiocytes with similar ingested foreign material, along with atheromatous emboli, and mild to moderate interstitial fibrosis. Treatment was supportive, including renal replacement therapy (RRT), with improvement in kidney function to the point of having adequate urinary output, no electrolyte derangements and no further need for RRT at discharge.

Discussion: In this case report, we compare our findings to other reported cases of hydrophilic polymer emboli to increase awareness of this under-recognized cause of organ dysfunction.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

137
Discussion: Pemetrexed is a second line agent that has been used to treat 84% of the second most common cancer in both men and women in the US. The most common adverse reactions are fatigue, skin desquamation, nausea, stomatitis, neutropenia and pharyngitis. A significantly less common adverse effect is AKI that can occur and if not identified can lead to acute renal failure. In our patient, his AKI is thought to be multifactorial from pre-renal due to decreased oral intake and intrinsic due to the toxicity of pemetrexed. Although aggressive fluid administration is imperative, the anti-folate effects of pemetrexed must be reversed with folic acid in order to prevent the patient from going onto dialysis. Prompt recognition of this adverse effect can lead to suitable treatment and recovery of his kidney function.

PO0284
An Unusual Presentation of Type 1 Cryoglobulinemic GN in Monoclonal Gamopathy of Undetermined Significance (MGUS)
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Introduction: Type 1 cryoglobulinemia can develop in the setting of monoclonal gammopathy of undetermined significance (MGUS) and can have renal involvement in a third of cases. We present an unusual case of Type 1 cryoglobulinemic glomerulonephritis (GN).

Case Description: An 83-year-old woman with a history of IgG Kappa MGUS presented with decreased urine output and nausea. During the previous six months, the patient was hospitalized three times for acute kidney injury (AKI) requiring dialysis. Two renal biopsies had been performed during those admissions, which showed GN with scant immune deposit. One glomerulus had intraluminal staining for IgG and Kappa suggesting a cryoglobulinemic GN secondary to her MGUS (Figure 1, A-C). She declined chemotherapy at the time, however, each time her renal function improved spontaneously and she was discharged without requiring dialysis. In the ED, her blood pressure was 182/69 but her vitals were otherwise normal. The physical exam was unremarkable. Labs were notable for sodium 122 meq/L, potassium 5.2 meq/L, creatinine 4.5 mg/dL, albumin 3.4 g/dL, low C3 and C4, and positive MPO-ANCA. The urinalysis showed 50 red blood cells, 15 white blood cells, and random urine protein > 2000mg/dL. Other serologic and infectious labs, including serum cryoglobulin, were negative. The renal ultrasound was normal. The patient’s renal function worsened and was started on dialysis. This time the patient agreed to chemotherapy and immunosuppression with the aim to prevent further recurrences of AKI. The patient was started on clone-directed therapy with cyclophosphamide, bortezomib, and dexamethasone. Plasma exchange therapy was also performed for the clearance of light chains. The patient’s renal function improved and she was discharged without requiring dialysis. Her two-month follow up creatinine was 1.08mg/dL.

Discussion: This case of type 1 cryoglobulinemic GN is unusual in that the patient developed cyclical but self-resolving episodes of AKI-D that was successfully treated with clone-directed therapy.

PO0285
A Case of Renal Papillary Necrosis in the Setting of Acute Pyelonephritis and Chronic NSAID Use
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Introduction: Renal papillary necrosis is an ischemic process that affects the renal papillae and inner medulla leading to acute kidney injury. Most common causes include diabetes mellitus often with urinary tract infection, sickle cell anemia, and analgesic use. It is histologically delineated by congealing necrosis of the renal papilla and medullary pyramids, and potentially acute liquefactive necrosis in the presence of infection. We report a case of renal papillary necrosis in the setting of acute pyelonephritis and chronic NSAID use.

Case Description: A 59-year-old Caucasian male with a history of hypertension, irritable bowel syndrome, hyperlipidemia who presented with 4 days of vomiting, diarrhea, decreased urinary output, and generalized weakness. He endorsed twice daily use of naproxen for the past couple months. Physical examination only notable for dry mucous membranes. Initial work-up demonstrated serum creatinine of 12.7 mg/dL (baseline 1.0 mg/dL), serum sodium level of 133 mmol/L, serum potassium level of 7.4 mmol/L, blood urea nitrogen 147 mg/dL. WBC count 30.5 x10^9/L, and urinalysis with pyuria, microscopic hematuria, and proteinuria. Further work-up showed urine culture...
with pan-sensitive Escherichia coli, sub-nephrotic proteinuria, and complete serologic workup only positive for serum protein electrophoresis. CT abdomen/pelvis without contrast did not demonstrate any hydronephrosis. A native kidney biopsy was performed and revealed diffuse tubulointerstitial inflammation with prominent intratubular white cell casts and areas of confluent parenchymal necrosis consistent with acute pyelonephritis leading to renal papillary necrosis. He completed a 7-day course of ceftriaxone for E. coli urinary tract infection and eventually required hemodialysis with no signs of kidney recovery upon discharge.

Discussion: Renal papillary necrosis is a rare disease entity and is underdiagnosed due to infrequent clinical presentation. Unfortunately, it could have potentially been diagnosed if undiagnosed, which is evident upon reviewing the current literature. By presenting this case, we highlight this unique presentation of renal papillary necrosis in a non-diabetic individual and urge clinicians to have a high index of suspicion and subsequently a low threshold for kidney biopsy to establish a diagnosis and improve patient outcomes.

PO0286

A Rare Case of Evans Syndrome with Systemic Lupus Erythematosus and Pulmonary Nocardirosis
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Introduction: Evans syndrome (ES) is a rare autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune-mediated thrombocytopenic purpura (ITP). The exact pathophysiology is unknown but is initiated by having autoantibodies attacking body’s own red blood cells and platelets.

Case Description: 20-year-old male with history of autoimmune dysregulation including SLE (diagnosed when he was 13). Evan’s Syndrome, class 5 lupus nephritis presented to the Hospital for difficulty breathing, dry cough and 30-pound weight loss. He was admitted to ICU for acute hypoxic respiratory failure requiring intubation. His lab work showed anemia, thrombocytopenia, AKI, ANA+, low C3, C4, elevated LDH, high uric acid, UA showing 3+ blood and 6 grams of proteinuria. A chest CT on admission also noted extensive LAD, splenomegaly, ground glass opacities and interstitial prominence in lungs. He underwent a lung biopsy which showed DAH. The patient was also treated with pulsed steroids, plasmapheresis and Cytosan. He also had MSAA bacteremia treated with antibiotics and rehab course complicated with pulmonarynocardirosis.

Discussion: Although ES is an extremely rare case, it is important to keep broad differentials as renal dysfunction is common from different pathologies. Usually the most common cause of AKI associated with ES is ATN from intravascular hemolysis and had widespread intratubular hemoglobin casts but it is essential to consider other etiologies as common cause of AKI associated with ES is ATN from intravascular hemolysis and had widespread intratubular hemoglobin casts but it is essential to consider other etiologies as in our case of previous lupus flare.

PO0287

Acute Myositis Complicated by Rhabdomyolysis in Setting of COVID-19 Infection in a Patient with Rosuvastatin: A Case Report
Anand Kumar, Anjali Muralideharnan, Yasir Lal. The University of Texas Medical Branch at Galveston, Galveston, TX.

Introduction: Viral illnesses are uncommon cause of rhabdomyolysis and AKI. A few cases of rhabdomyolysis have been reported with COVID-19 infection previously. However, Covid-19 presenting solely with rhabdomyolysis in absence of respiratory symptoms is rare. There is also paucity of data supporting steroids use in such cases. We present a case of COVID-19 related rhabdomyolysis who recovered in response to steroid therapy.

Case Description: This is a 78-year-old female with history of dyslipidemia and chronic kidney disease III who presented with generalized weakness and myalgias. Home medications included Rosuvastatin. She was diagnosed with Covid-19 virus. Rosuvastatin was held, however her myalgia muscle weakness worsened, and she was no longer able to stand without support. She denied fever, chills, rash, or respiratory symptoms. At presentation, physical exam revealed diffuse muscle tenderness and diminished strength: 1/5 and 2/5 on proximal bilateral lower and upper extremities respectively. WBCC’s 11.13. K 5.7, Cr 5.72, ANA, HMG CoA reductase antibody assay and myositis panel (SSA-52, SSA-60, Smith/RF antibodies, anti-SMRNP, anti-SSA, anti-SSB, & RF) were negative. CK 14, 085 U/L, granular and muddy brown casts on urine microscopy. Lower extremities MRI showed bilateral muscular edema, EMG was consistent with myopathic changes with predominant type 2 fiber atrophy, and mild neurogenic changes, consistent with rhabdomyolysis. Immunohistochemistry showed rare peripheral B lymphocytes and plasma cells. CK continued to rise and peaked at 99,383 U/L. At admission serenaturner was nil. This resulted in a significant improvement in CK and creatinine over the next few days.

Discussion: Viral myositis leading to rhabdomyolysis and AKI as the primary presentation of Covid-19 infection is uncommon. In our case, a short course of steroids, resulted in quick recovery. Early recognition and diagnosis followed by intervention can prevent further muscle and renal damage and can prevent hospital stay and reduced morbidity significantly. Cureus. 2020 Oct; 12(10): e11886. Akanesara et al. Solis, J. G. et al. The american journal of tropical medicine and hygiene, 103(3), 1158-1161.

PO0288

AKI Induced by Oral Semaglutide Leading to Metformin-Induced Lactic Acidosis
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Introduction: Lactic acidosis is a known complication of metformin treatment, especially in the context of elevated creatinine. This is a patient on chronic metformin therapy who developed actue kidney injury and lactic acidosis after initiation of semaglutide.

Case Description: A 77-year-old male with a history of non insulin dependent type 2 diabetes, hypertension and hyperlipidemia brought in for altered mental status. Patient had been prescribed metformin for years with any complications. Vitalis: temp 91.2 F, BP 117/27, RR 25, spO2 98% on room air. Physical examination was unremarkable including no edema however was oliguric. On admission patient had a Na 130 mmol/L, Potassium 6.1 mmol/L, Chloride 76 mmol/L, CO2 5 mmol/L, Anion gap 49 mmol/L, Blood Urea Nitrogen 65 mg/dL, Creatinine (Cr) 6.4 mg/dL (baseline Cr 1.3 mg/dL), lactate 22.6 mg/dL, and a Venous blood gas pH of 6.8, Ammonia 245 mmol/L, with normal liver enzymes, COVID PCR negative. CT Abdomen without contrast and Chest x-ray did not show any acute process. Treatment: Patient was admitted to Intensive Care Unit, Semaglutide and Metformin discontinued. He was started on Continuous Renal Replacement Therapy (CRRT) then transitioned to conventional hemodialysis. Patient made remarkable recovery. At the time of discharge patient was off diaylsis with Cr 1.1 mg/dL.

Discussion: Semaglutide is a glucagon-like peptide 1 receptor agonist (GLP-1 agonist). GLP-1 agonist’s have gained popularity in the outpatient setting for management of Type 2 diabetes mellitus. Semaglutide is FDA approved for type 2 diabetes mellitus. There is limited information regarding its use in chronic kidney disease. Reports of AKI requiring dialysis in available studies show incidences of AKI that present in the placebo groups. The high acuity of disease that occurred in the above patient was compounded by metformin toxicity. Many future patients prescribed semaglutide will be on metformin. Information such as this could require physicians to use extra caution as they prescribe this medication combination, especially in the elderly population. There is also paucity of data supporting steroids use in such cases.

PO0290

Continuous Renal Replacement Therapy: A Reversible Cause of Thrombocytopenia
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Introduction: Thrombocytopenia is frequently encountered in critically ill patients. Whether present on admission or acquired during hospitalization, inadequate platelet counts are an independent risk factor for patient morbidity and mortality in the Intensive care unit. TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

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139
Care Unit. Continuous renal replacement therapy is a lesser known cause of acquired thrombocytopenia.

Case Description: In this retrospective case series, four patients that developed thrombocytopenia while receiving continuous renal replacement therapy (CRRT) in the Intensive Care Unit were evaluated. The temporal relationship between onset of thrombocytopenia, timing of CRRT, and subsequent trend in platelet counts were analyzed. The patients had a variety of risk factors for thrombocytopenia including septic shock, presence of chronic kidney disease, mechanical support therapies, and anticoagulation with heparin. Despite these characteristics and interventions, each of the patients demonstrated a pronounced drop in platelet count within 72 hours of initiating CRRT, with a subsequent improvement in platelet count following cessation of CRRT.

Discussion: Thrombocytopenia is a complication of critical illness that, in extreme cases, can lead to further cost and resources to evaluate and possibly delay necessary interventions. In patients requiring renal replacement therapy, clinicians must be cognizant that continuous modalities are a potential source of thrombocytopenia. Nephrologists are responsible for knowing all potential adverse outcomes of the procedure of dialysis. Educating other health team members of these risks is part of that responsibility.

Data

CRRT = Continuous Renal Replacement Therapy

P00291
Successful Utilization of Hemodialysis for Treatment of Vancomycin Nephrotoxicity

Tushar Thakur, Mingyue He, Waqas Ahmad Khan, Ziauddin Ahmed, Iris J. Lee. Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: Vancomycin is frequently used as empiric antimicrobial therapy for septic shock. At supratherapeutic levels, vancomycin can potentially cause nephrotoxicity. Nephrotoxicity often resolves on discontinuing the medication, but recovery may be prolonged and injury severe, requiring dialysis. The role of hemodialysis is limited, and evidence suggests that standard membrane dialysis provides poor clearance. However, the current use of high flux dialysis can eliminate vancomycin faster, promoting quicker renal recovery.

Case Description: A 49-year-old female admitted for septic arthritis received vancomycin 1.5 g/day and piperacillin/tazobactam. Incidence of AKI increases with higher daily dosage (>4 g/day), coexisting with elevated vancomycin levels and the absence of an alternative explanation for rising creatinine. Vancomycin levels can result from decreased GFR from AKI. The rise of creatinine to 18 ug/ml. Gradually her urine output improved with resolution of AKI.

Successful Utilization of Hemodialysis for Treatment of Vancomycin Nephrotoxicity

P00292
Atypical Hemolytic Uremic Syndrome: A Case Report

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Introduction: Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative hemolytic anemia, and end-organ damage. The most common forms of thrombotic microangiopathies are Shiga toxin-producing Escherichia coli mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome. The atypical hemolytic uremic syndrome occurs due to genetic and acquired mutations in complement regulatory factors and to complement activation factors in the immune system, mainly the alternative pathway. Clinical manifestations and outcomes differ with the prevalent mutations of the patient. Currently, available treatment modalities are therapeutic plasma exchange and a monoclonal antibody against C5, eculizumab.

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Patient with Refractory Acquired Thrombotic Thrombocytopenic Purpura Treated with a Novel Agent Caplacizumab

Pranay Sharma, Jonathan Lebowitz. Rutgers The State University of New Jersey, New Brunswick, NJ.

Introduction: Acquired or immune-mediated TTP is characterized by thrombocytopenia and anemia caused by autoantibody-mediated inhibition of the von Willebrand factor (vWF) cleaving protease, ADAMTS13. This results in a microangiopathic hemolytic anemia and severe thrombocytopenia, resulting in tissue ischemia, multiorgan failure, and, potentially, death. Up until now, treatment for TTP included therapeutic plasma exchange (TPE) and immunosuppression. Recently, caplacizumab, the first targeted nanobody based therapeutic agent that prevents adhesion of platelets to vWF, has been approved for use in acquired TTP. We present a case of acquired TTP that was refractory to high dose, steroids, therapeutic plasma exchange (TPE) and rituximab but responded well to caplacizumab.

Case Description: A 53-year-old man with HIV, complicated by cryptococcal meningitis and PCP pneumonia, intermittent confusion, headache, and multiple falls, presented with anemia, thrombocytopenia, an elevated LDH, and a peripheral blood smear with numerous schistocytes with acute kidney injury with an initial serum creatinine of 1.7 mg/dl which peaked up to 5.5 mg/dl. Further testing revealed a positive ADAMTS13 inhibitor with high titer of 3.4 and less than 5% ADAMTS13 enzyme activity, consistent with TTP. He was treated with high dose steroids, TPE, and rituximab but did not respond. He was initiated on caplacizumab on hospital day 14 and by day 18 his platelet counts began to normalize and mentation improved. He suffered only mild epistaxis as a side effect from caplacizumab. In span of few days, his neurologic symptoms resolved and he was discharged home to complete thirty days of caplacizumab treatment. At the time of follow up, he remained well and continued to have normal ADAMTS13 activity. Kidney function improved post caplacizumab to 0.8 mg/dL.

Discussion: Although conventional therapy has reduced the mortality of TTP, it is not always effective and there are a fair number of cases refractory to conventional treatment. Caplacizumab, the first nanobody-based therapeutic agent, has shown marked efficacy in treating TTP and its complications and is a therapeutic option for patients with refractory TTP.

Use of Eculizumab in Thrombotic Microangiopathy (TMA) Associated with PM/SCL100 and 75 and RP 155 Antibody-Positive Autoimmune Overlap Syndrome with Renal Crisis

Jahanzeb Khan,1 Heba Mousea,1 Mujtaba Sarwar,1 Ramya Bachu,1 Anum Syed,1 Sehrish W. Bakshri,12 Faikher Ijaz,12 Baptist Health Medical Center - North Little Rock, North Little Rock, AR;1 Kidney Care Center, Little Rock, AR.

Introduction: TMA with associated PM/SCL100 & 75 and RP 155 antibody positive Autoimmune Overlap Syndrome with renal crisis has a very poor prognosis and limited therapeutic options. Use of Eculizumab has been reported in only a few cases in literature.

Case Description: A 44 years old female with hypertension and Raynaud’s phenomenon presented with hypertensive emergency, recent sclerodactyly, hemolytic anemia, thrombocytopenia and renal failure. Routine serum markers including DsDNA Ab, complement, ANCA, SSB, Scl 70 Ab, Anti-centromere Ab, RNA polymerase 3 Ab, U-3 RNP Ab, lupus anticoagulant, beta 2 glycoprotein Ab and ADAMTS-13 were all negative. Pulse Steroids and plasmapheresis were initiated due to concern of aHUS. Renal biopsy showed onion skinning of arterioles with near complete occlusion of arterioles as shown in the figure. ACEI was added. Later she was found to have positive PM/SCL 100 & 75 and RP 155 antibodies. She was started on Eculizumab secondary to poor hematological response to the above measures. Our patient showed improvement of her thrombotic microangiopathy which helps to support the use of this drug in this rare disorder.

Discussion: Very limited therapeutic options are available for cases of Autoimmune Overlap Syndrome. Our use of Eculizumab; an anti-C5d monoclonal antibody, also supports the benefits of blocking the activation of the classical complement pathway which may suggest the underline mechanism in this disease process.

Use of Eculizumab in Thrombotic Microangiopathy (TMA) Associated with PM/SCL100 and 75 and RP 155 Antibody-Positive Autoimmune Overlap Syndrome with Renal Crisis

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Discussion: Very limited therapeutic options are available for cases of Autoimmune Overlap Syndrome. Our use of Eculizumab; an anti-C5d monoclonal antibody, also supports the benefits of blocking the activation of the classical complement pathway which may suggest the underline mechanism in this disease process.
Discussion: Eosinophilic cystitis is a rare disease. Association with history of allergy and urinary tract infection is variable. Radiological finding are usually consistent with thickened bladder wall. In a case series of 10 Chinese patients, only one patient had bilateral hydroureteronephrosis. Medical treatment is mainly by non-steroidal anti-inflammatory drugs, corticosteroids, anti-histamines and antibiotics. Surgical modalities of treatment include transurethral resection of the lesions, partial cystectomy or total cystectomy. Response to different modalities of treatment is variable.

PO0299
Treatment of FSGS and Hemophagocytic Syndrome with Tocilizumab
Daniel W. Shields, Michael Dore, Richard A. Plasse. Naval Medical Center Portsmouth, Portsmouth, VA.

Introduction: Hemophagocytic syndrome (HPS) is a rare and often life-threatening condition characterized by an overre ac tation of the immune system. HPS has a variety of triggers including: malignancy, infection, and rheumatologic conditions. Clinically, it is characterized by acute fever, cytopenia, lymphadenopathy, hepatosplenomegaly, intravascular coagulation, hyperferritinemia, and elevated liver associated enzymes. We present a case of reactive HPS complicated by focal segmental glomerulosclerosis (FSGS) secondary to a febrile gastrointestinal illness in an otherwise healthy 36 year old male.

Case Description: A 36 year old male presented to the ER with a 3 day history of fevers, nausea, vomiting, and diarrhea. Labs demonstrated hyponatremia to 126 and acute renal injury. He was admitted for presumed viral gastroenteritis and treated supportively. He then developed elevated liver associated enzymes and pancytopenia. An infectious work up was unrevealing. Flow cytometry was negative for lymphoma or leukemia. Ferritin was elevated at 4450 ng/mL. A bone marrow biopsy demonstrated hemophagocytosis. He then developed multiple pulmonary embolisms, lower extremity edema, new onset ascites, and nephrotic range proteinuria. A renal biopsy showed diffuse podocyte effacement with rare Focal Segmental Glomerulosclerosis (FSGS) with collapsing features and no immune complexes. His IL-2 soluble receptor was elevated at 2710 pg/mL. He was diagnosed with HPS, started on prednisone 1 mg/kg then transitioned to tocilizumab.

Discussion: The pathogenesis of HPS is excessive activation and proliferation of T lymphocytes and macrophages leading to phagocytosis of hematopoietic cells in the bone marrow and hypersecretion of proinflammatory cytokines causing multi organ dysfunction. Due to the difficulty in diagnosis, the Hscore was developed to estimate the probability of HPS. Our patient’s Hscore was 209 equating to an 88-93% probability. Renal dysfunction occurs in ~16% of patients with HPS with symptoms ranging from hyponatremia to renal failure. Nephrotic syndrome is most commonly due to collapsing FSGS. Case reports have demonstrated the use of tocilizumab in the treatment of FSGS from other etiologies, but treatment of HPS and FSGS has not been reported. Our patient had resolution of his nephrotic syndrome with immunosuppressive therapy with steroids and remain in remission on tocilizumab.

PO0300
Transition of Portal Vein Doppler Waveform with Improving Venous Congestion: A Case Study
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Introduction: The diagnostic accuracy of physical examination, weight, laboratory parameters such as BNP is limited for the assessment of fluid status. Point-of-Care Ultrasonography (POCUS) is emerging as a valuable bedside tool for evaluation of hemodynamics at the bedside. Herein, we present a case which illustrates the practical utility of portal vein Doppler.

Case Description: A 78-year-old woman with a history of heart failure (HF) with reduced EF (~20%) and pulmonary hypertension was brought to the hospital for altered mental status. She was found to have acute kidney injury (AKI) with a serum creatinine of 2.2 mg/dL (baseline ~1.1) and urinalysis was suggestive of UTI. Urine sodium and chloride were ~20 mmol/L. Antibiotic therapy was started; AKI was presumed to be secondary to volume depletion as her diuretic regimen was recently intensified. There was no significant weight gain. Administering physician noted mild pedal edema and no}

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Case Description: A 30-year-old previously healthy male presented to the ED with complaints of nausea and vomiting. He reported intentional caloric restriction and intense exercise over the past month, along with using the-counter oral Oxandrolone. Labwork revealed AGMA and ketosis (CO2 17.2mmol/L, AG 24.4 mmol/L, β-hydroxybutyrate 48.97 mg/dL) elevated Creatinine (2.8 mg/dL). Glucose, LFTs and CK-PK were normal. UA revealed 9 ketones, Protein 100 mg/dL. RBC 10-25. US and CT of abdomen and pelvis were unremarkable. He was started on IVF and anti-emetics with resolution of symptoms and starvation ketoadiposis. Renal function, however, progressively worsened. BUN/Cr < 20, FeNa 1.4% and no improvement with IVF was noted. Further work up included C3/C4 levels, Figure 1: Rhomboid shaped calcium oxalate crystals distending renal tubule without attenuated and disruption of epithelial lining. Right: Calcium oxalate crystals characteristically birefringent under polarized light microscopy.

Discussion: TIN is associated with a number of systemic illnesses inclusive of pSS. Renal disease in pSS is as high as 42%, with TIN accounting for approximately 10-20% of cases. TIN usually presents after the initial diagnosis of pSS but in our patient it occurred concurrently with the diagnosis. The renal involvement in pSS is usually chronic and it typically shows membranoproliferative TIN with minimal glomerular involvement. However, there is a wide range of renal pathology including TIN to MPGN, membranous nephropathy, focal segmental GN. Even though renal impairment does not typically precede pSS it is imperative to biopsy as early as possible so that treatment can be initiated to prevent chronic disease.

PO0305
Excess Vitamin C Leading to Hyperoxaluria and AKI
Katherine Julian, Catherine Abendroth, Ali M. Zebi, Amanda A. Karasinski, Rohit Jain. Penn State Health Milton S Hershey Medical Center, Hershey, PA.

Introduction: Secondary hyperoxaluria is caused by increased ingestion of oxalate or oxalate precursors, increased oxalate enteric absorption due to fat malabsorption, or changes in intestinal microflora and can manifest as end stage renal disease or hyperoxaluric nephropathy.

Case Description: A 55-year-old female with history of hyperparathyroidism and hyperoxaluric nephropathy (not med compliant) presented with myxedema coma secondary to uncontrolled hypothyroidism. Initial workup revealed elevated potassium (7mmol/L), BUN (194mg/dL), SCR (35mg/dL) and TSH (>100uIU/mL). She was given IV levothyroxine, IV lithothing, insulin, calcium glutamate and hydrocortisone, and started hemodialysis in the setting of acute kidney injury (AKI) with no known underlying CKD, nephrolithiasis or nephrocalcinosis. Autoimmune, gastrointestinal, and hepatobiliary AKI etiologies were ruled out. A renal biopsy revealed renal oxalosis (Fig 1). Investigation of possible secondary causes of renal oxalosis revealed consumption of large quantities of vitamin C in hopes of preserving her health during the COVID-19 pandemic. The patient remained dependent on hemodialysis was discharged on levothyroxine 150mcg daily. Unfortunately, an ultrasound revealed intrauterine fetal demise. She received 2 units of platelets and underwent an uneventful delivery. Following delivery, all parameters (table 1). Unfortunately, an ultrasound revealed intrauterine fetal demise. She received 2 units of platelets and underwent an uneventful delivery. Following delivery, all parameters improved (table 1). Two days post-delivery, ADAMTS-13 level returned at <2%. She was started on high dose prednisone and received 4 sessions of plasmapheresis. ADAMTS-13 antibody was later found to be negative.

Discussion: TTP is caused by deficiency of ADAMTS-13 metalloproteinase which cleaves the von Willebrand factor. Low activity of ADAMTS-13 (20-40%) is seen in patient with preeclampsia, eclampsia, HELLP syndrome and pregnancy associated hemolytic uremic syndrome. The enzyme level will decrease to less than 20% only in pregnancy associated TTP. Though TTP in the general population is mostly immune in nature, 24% of cases of pregnancy associated TTP are hereditary. Delivery has been shown to achieve rapid remission in many cases. Most authorities recommend initiation of plasmapheresis with TMA and pregnancy when platelet count is less than 30 with TTP unmasked by pregnancy. TTP has a 100% risk of relapse with future pregnancies making it essential to differentiate the two entities for appropriate management of future conceptions which requires plasma exchange starting early in pregnancy.

Table 1

Figure 1: Left: Rhomboid shaped calcium oxalate crystals distending renal tubule with attenuated and disruption of epithelial lining. Right: Calcium oxalate crystals characteristically birefringent under polarized light microscopy.

PO0306
Candida parapsilosis Endocarditis Presenting as Acute Glomerulonephritis: A Case Report
Tai Truong, Devin Lee, Martin Sedlacke. Dartmouth-Hitchcock Health GraniteOne, Lebanon, NH.

Introduction: Candida species is an uncommon cause of left sided endocarditis that traditionally associated with high morbidity rate. In a few rare cases, Candida endocarditis is reported as a cause of acute glomerulonephritis (GN). Here we present a case of Candida parapsilosis endocarditis that presented as acute glomerulonephritis.

Case Description: A 52 y/o Caucasian female with history of antiprostaphilid syndrome, intravenous drug use history on suboxone who presented with 3 weeks of night sweats, weight loss, and 3+ blood. A urine dipstick showed >300 protein and 3+ blood. A spot urine protein to creatinine ratio was 4.5. The urine sediment showed granular and hyaline casts, many RBC of normal morphology and rare acanthocytes. The C3 level was mildly decreased at 60 and C4 level normal at 14. She had

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143
mildly elevated ANA at 1:80 and negative double strand DNA, smooth muscle antibody level, PR3/MPO and extractable nuclear antigen antibody including SSA/SSB, RnF, ScL-70 and Jo-1 antibody level. A CRP was 33 and ESR was 47. Blood cultures revealed Candida parapsilosis. MRI spine with inflammatory changes of L4-L5 suggesting osteomyelitis. Patient received micafungin but remained persistently fungemic. A TEE revealed a large mitral valve vegetation. While under evaluation for mitral valve surgery, she suffered from a large right MCA stroke and deceased within 48 hours from brain herniation. No autopsy performed due to family’s request.

Discussion: Fungal associated GN is a rare clinical entity that usually mentioned only as a footnote in textbooks. The mechanism of kidney injury is likely immune complex deposition. Given the high mortality rate with Candida endocarditis and its associated complications, heightened clinical suspicion and early aggressive treatment with antifungal and surgery are important. Corticosteroids in one case report improved renal function indicating a possible role in patients with controlled infection.

PO0307
Linezolid-Associated Interstitial Nephritis
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Introduction: Acute Interstitial Nephritis (AIN) accounts for 15-27% of renal biopsies performed for Acute Kidney Injury (AKI). Drug induced AIN remains the most common cause. We present a case of Linezolid induced AIN, a rare entity.

Case Description: Elderly male patient with type 2 diabetes, hypertension and normal renal function was initiated on linezolid for osteomyelitis. Two weeks later, he reported a maculopapular rash on his arms and chest. Labs were significant for a serum creatinine (Scr) of 3.8mg/dl. Immunochemical and infectious work up for AKI was unremarkable. Scr continued to increase to 7.2mg/dl and absolute serum eosinophil count was 1800 cells/ microliter. Interstitial nephritis was suspected and empiric prednisone was initiated. Renal function continued to increase to 7.2mg/dl and absolute serum eosinophil count was 1800 cells/ microliter. Interstitial nephritis was suspected and empiric prednisone was initiated. Renal function remained stable. Linezolid associated Interstitial Nephritis is rare, and only 4 cases have been reported in the literature. As the prevalence of Methicillin Resistant Staphylococcus Aureus increases, we must be wary of this complication before initiating treatment. Renal function must be monitored, and prompt initiation of steroids can ensure improvement of renal function.

Discussion: This patient developed a rash and interstitial nephritis after the initiation of linezolid. He reported no Non-Steroidal Anti-Inflammatory Drug (NSAID) intake and was on vancomycin and piperacillin- tazobactam for less than 48 hours, during which renal function remained stable. Linezolid associated Interstitial Nephritis is rare, and only 4 cases have been reported in the literature. As the prevalence of Methicillin Resistant Staphylococcus Aureus increases, we must be wary of this complication before initiating treatment. Renal function must be monitored, and prompt initiation of steroids can ensure improvement of renal function.

PO0308
Rifampicin: An Infrequent Cause of AKI
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Introduction: Rifampicin is used to treat Mycobacterium infection. Hypersensitivity reaction to rifampicin resulting in acute kidney injury (AKI) is infrequent. Here we describe rifampicin hypersensitivity in a patient presenting with AKI who was treated for Mycobacterium marinum infection.

Case Description: A 43 year old male was treated with Rifampicin for Mycobacterium marinum infection 3 years ago. He recently injured his hand and took two pills of Rifampicin leftover from 3 years ago to prevent another infection. He took them about 12 hours apart and a few hours after taking the second pill he developed severe nausea, vomiting, flank pain and dark colored urine. He presented to emergency department and labs showed elevated LDH(lactate dehydrogenase) and bilirubin, thrombocytopenia, anemia and elevated creatinine. He was transferred to our hospital for further management. Upon arrival creatinine was 7.5mg/dl. Bilirubin had normalized and haptoglobin was in normal range. ADAMTS13 level was 56%. Peripheral smear did not show schistocytes. He underwent kidney biopsy which showed moderate acute tubular injury and focal thrombotic microangiopathy. It was determined that he had AKI from type 2 hypersensitivity to Rifampicin. His creatinine continued to worsen to 18mg/dl before improving. He did not require renal replacement therapy. On follow up three weeks later, his creatinine had improved to 1.7mg/dl.

Discussion: Rifampicin hypersensitivity can manifest with hepatitis, hemolytic anemia and AKI. It is most often seen when the drug is re-administered or used intermittently. The outcome of AKI is usually favorable after discontinuation of the drug, with most patients achieving full recovery within 90 days. As the hypersensitivity reaction is infrequent, prompt recognition and withdrawal of drug is important to prevent irreversible injury.
PO0310
Precipitous AKI: A Unique Form of AKI by Vancomycin
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Introduction: Vancomycin-associated acute kidney injury (VA-AKI) is a well-known entity. With improvement in formulations of vancomycin (vanc), its incidence has decreased, however it remains a risk factor of AKI especially when used in combination with other nephrotoxic agents. We present a case of VA-AKI that represents a unique pattern of kidney injury, known as “precipitous AKI”.

Case Description: A 23-year-old male presented to the emergency room with fever & body aches for 1 day. He was getting chemotherapy for acute lymphocytic leukemia; last received cyclophosphamide 10 days ago. He was tachycardic. Physical exam was unremarkable. His absolute neutrophil count was 0.5x10^9 cells/dl. He was admitted & started on IV vanc & Piperacillin/Tazobactam. On the 4th day of admission (DoA), he developed AKI with rise in blood urea nitrogen (BUN) and creatinine (Cr) to 37mg/dl and 3.6mg/dl, (baseline of 12mg/dl & 0.9mg/dl) respectively. Urine sediment showed granular casts suggestive of tubular injury. Vanc was stopped; until then he had received a cumulative dose of 5grams. Cr peaked to 8mg/dL on the 8th DoA. The rise in BUN was discordant which only rose to 52mg/dL. The patient never developed oliguria either. His BUN and Cr improved thereafter and he was discharged. The BUN and Cr were normal on repeat testing done 2 weeks later.

Discussion: Precipitous AKI is the term coined by Velez et al. which appears to be the first description of this entity. To our knowledge, only a handful of cases have been reported. It is seen in patients who receive high cumulative dose of vancomycin and manifests as rapid rise in Cr (more than 2.5mg/dL in a day) while in other causes of AKI the rise of Cr is between 1-1.5mg/dL. The relative rise in BUN does not match that of Cr. The patients do not develop oliguria, & cystatin C is usually normal. These observations support the notion that glomerular filtration is not affected, and is postulated to be caused by tubular toxicity that effects the tubular secretion of Cr. Further studies are needed however.
**PO0313**

**Unexplained AKI: Never “Brush” Off the Role of a Renal Biopsy**

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**Introduction:** Anti-Brush Border Antibody Disease (ABBAD) is a rare condition typically seen in elderly individuals and presents with acute kidney injury (AKI) and subnephrotic proteinuria. Patients often progress rapidly to ESKD despite treatment.

**Case Description:** A 73-y/o man with a PMH of HTN, a-fib and CKD (serum creatinine SCr 1.5 mg/dl 4 mo ago and 2.3 mg/dl 2 mo ago) was found to have a SCr of 3.2 mg/dl. His medications were tamsulosin, apixaban, losartan and metoprolol tartrate. He denied NSAID usage. His vital signs were normal and his physical exam was unremarkable. His urinalysis was significant for 2+ protein without blood. He had an elevated urine protein/Cr ratio at 1.5 g/g. Serological and infectious workups were negative. A renal ultrasound was normal. A renal biopsy demonstrated 50% global sclerosis with remaining glomeruli normal. There was moderate interstitial fibrosis and tubular atrophy. The immunofluorescence and electron micrographs are shown in Fig 1a and 1b. Specific IF staining for lipoprotein-related protein 2 (LRP2) was positive in the tubular basement membrane (TBM), consistent with a diagnosis of ABBAD. Because of his advanced age he was treated with 60 mg of prednisone alone with no improvement. Specific IF staining for lipoprotein-related protein 2 (LRP2) was positive in the tubular basement membrane (TBM), consistent with a diagnosis of ABBAD. Because of his advanced age he was treated with 60 mg of prednisone alone with no improvement. This approach requires a low renal threshold for biopsy in AKI. It is however unknown if early treatment can alter the typical abysmal renal outcome.

**Discussion:** ABBAD occurs from formation of IgG antibodies against low density lipoprotein-related protein 2 (LRP2) megalin which deposit on the tubular BM of the PCT. ABBAD can be induced by lamotrigine use. The patients had few commonalities other than lamotrigine intake.

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**PO0314**

**Vitamin C, CKD, and Roux-en-Y: A Dangerous Combination**

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**Introduction:** Patients who have undergone bariatric procedures can be at increased risk for acute kidney injury (AKI) due to oxalate nephropathy; therefore, it is important that there is an awareness of other risk factors for this condition in this patient population. In particular, high doses of vitamin C should be avoided.

**Case Description:** A 74-year-old female, who had a Cr of 0.8 mg/dl a year prior, with a history of Roux-en-Y gastric bypass surgery in 2016, recurrent nephropathiasis, and an atrophic right kidney was advised to go to the hospital after outpatient laboratory data revealed a Cr of 8.7 mg/dl. The patient had been taking Vitamin C 1000 mg daily. An initial evaluation did not reveal an etiology of AKI and her renal function did not improve with 48 hours of IV fluids. Hemodialysis was initiated for uremic symptoms. The patient underwent a biopsy (Figure 1) which showed severe acute tubular injury, mild interstitial fibrosis and tubular atrophy, and significant tubular calcium oxalate crystal deposition. At the time of discharge, she had poor creatinine clearance and remained on hemodialysis.

**Discussion:** AKI related to oxalate nephropathy can be viewed as a confluence of pre-disposing conditions, risk factors, and exposures. Any single case may have one or more of these issues; this case is remarkable in that it encompasses multiple factors: 1. A pre-existent history of calcium oxalate stones, 2. A markedly atrophic right kidney, with a suspicion of chronic kidney disease and a reduced excretory capacity, 3. Prior Roux-en-Y gastric bypass resulting in increased absorption of oxalate, 4. Supplemental vitamin C intake, 5. Pyridoxine deficiency which limits the body’s ability to “detoxify” oxalate. Unfortunately, oxalate nephropathy is associated with poor renal outcomes; therefore, patients with multiple risk factors for this condition should be appropriately counseled and closely monitored.

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**PO0315**

**Lamotrigine-Induced Acute Interstitial Nephritis**

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**Introduction:** Medications such as penicillins, cephalosporins, vancomycin, ibuprofen, and ketorolac are the most common cause of acute interstitial nephritis (AIN), accounting for more than 75% of cases. Recently, antiepileptic drugs such as lamotrigine have been reported to cause AIN. Here, we report a case of a 39-year-old female who was on lamotrigine and admitted to the hospital with abdominal pain and acute renal failure.

**Case Description:** A 39-year-old female with a history of Hepatitis C, history of meth and heroin abuse, overactive bladder, hypothyroidism, and bipolar disorder presented to the emergency department with a week of abdominal pain. In the emergency department, she complained of nausea, constipation, and five days of hematuria. The patient was admitted after labs showed BUN/Cr of 48/3.69. Two weeks prior to presentation, she was started on lamotrigine 100 mg daily, which was held upon admission. Patient was started on IV fluids but her condition acutely worsened with thrombocytopenia, anemia, and leukopenia. She was started on methylprednisolone 500 mg IV daily due to concern for AIN vs vasculitis. Her blood and urine cultures resulted positive for E. coli, and she was subsequently started on IV ceftriaxone. The patient underwent a left kidney biopsy demonstrating AIN without crescentic glomerulonephritis, which was likely an allergic reaction secondary to lamotrigine use. Her biopsy also showed neutrophilic infiltration, likely secondary to pyelonephritis. She was discharged in stable condition on prednisone oral 20 mg daily.

**Discussion:** In summary, we present an adult patient on lamotrigine who was admitted due to acute renal failure. There have only been four reported cases of AIN induced by lamotrigine use. The patients had few commonalities other than lamotrigine use, but notably half of them were being treated for bipolar disorder. Our patient had a history of drug abuse with uncertainty on last use, which could represent another cause of

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
her AIN. After cessation of lamotrigine and treatment with methylprednisolone 500 mg IV, her laboratory findings improved; renal biopsy confirmed AIN. Our case is significant because it substantiates the use of corticosteroids management of lamotrigine-induced AIN.

**PO0316**

A Case of Abrupt Anuria from Bilateral Kinked Ureters

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**Introduction:** Urinary tract obstruction is a well-known cause of reversible AKI. In patients with 2 functioning kidneys, bilateral ureteral obstruction is rare and unilateral ureteral obstruction rarely causes anuria and often does not result in a noticeable worsening of renal function. Here we describe a case of abrupt anuria and severe AKI associated with bilateral kinked ureters resembling parenchymal renal failure.

**Case Description:** A 58-year-old female with metastatic epithelioid mesothelioma underwent debulking peritoneectomy, bilaterial salpingo-oophorectomy, and omentectomy with hyperthermic intraperitoneal chemotherapy with cisplatin at 50 mg/m2. Bilateral ureteral catheters were placed preoperatively to avoid ureteral injury during surgery. The catheters were removed on post-operative day (POD) 0. Post-operative course was initially uncomplicated with stable renal function and more than 2L urine output a day. On POD 2, she was noted to have abrupt anuria despite the presence of a functioning Foley catheter. Her creatinine increased from 0.7 mg/dL to 2.3 mg/dL. Renal ultrasound revealed normal sized, echogenic kidneys with mild bilateral hydronephrosis. A CT cystogram with contrast was negative for a urinary leak. On POD 3, she remained anuric. At this point there was concern for a dense ATN caused by cisplatin and initiation of hyperhydration. On POD 4, the patient was transferred to the intensive care unit, which revealed bilateral ureteral kinking (see image). Bilateral ureteral stents were placed with brisk urine output noted intraoperatively and her renal function improved back to baseline.

**Discussion:** Obstruction can occur at any point in the urinary tract but tends to only cause anuria if obstruction occurs below the level of the bladder for patients with 2 functioning kidneys. Obstruction at the level of the ureter generally does not cause anuria and often does not result in a noticeable worsening of renal function. Here we describe a case of abrupt anuria and severe AKI associated with bilateral kinked ureters resembling parenchymal renal failure.

**PO0317**

Acute Interstitial Nephritis Secondary to Cocaine Use


**Introduction:** Renal failure resulting from cocaine use disorder is well documented with etiology ranging from rhabdomyolysis, vasculitis, thrombotic microangiopathy and rarely acute interstitial nephritis, although unclear underlying mechanisms.

**Case Description:** A 33-year-old African American female with history of bipolar disorder alcohol, crack, cocaine use disorder presented with generalized fatigue and dyspnea for the past 4 days requesting inpatient detox. Home medications were disulfiram, suboxone, and clonazepam. The patient was a heavy smoker with a history of intravenous drug use, non compliant with disulfiram. On exam, vital signs were stable, she was alert, oriented, and responding to questions appropriately. The patient had a history of drug use disorder and is on a stable regimens of methadone and buprenorphine. She denied any drug use in the past 4 days and was on withdrawal.

**Discussion:** The commonly used antibiotic trimethoprim/sulfamethoxazole (TMP/SMX) is known to cause AKI. AKI induced by TMP/SMX can occur through various mechanisms, such as acute interstitial nephritis, crystalluria, acute tubular necrosis, and “pseudo”-AKI due to inhibition of proximal tubular secretory organic cation transporters.

**PO0318**

Uric Acid Crystallopathy Associated with Trimethoprim/Sulfamethoxazole (TMP/SMX) Use in a Patient with Gout

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**Introduction:** Elevated Creatinine (Cr) without AKI can be seen due to increased production or decreased clearance of uric acid, decreased tubular secretion of Cr and uric acid. We report a patient who presented with pseudo AKI due to delayed urine leak post prostatectomy.

**Case Description:** A 53-year-old male with PMH of hypertension, mixed connective tissue disease and prostate cancer was admitted to our hospital 6 weeks after prostatectomy due to AKI noted during post op follow up visit. He had abdominal pain for which he was taking naproxen, nausea and oliguria. Labs showed a Cr 6.58 mg/dL (baseline 1.1 mg/dL), proteinuria, hematuria and pyuria. A CT of his abdomen showed fluid in his pelvis and no hydronephrosis. His Cr worsened despite supportive care. Serum uric acid level was 11.7 mg/dL, with an elevated fractional excretion of uric acid 5.4 mg/dL.

**Discussion:** Uric acid crystallopathy, uricosuria, and hypouricemia associated with SMX and/or TMP have been previously reported in the literature. It seems appropriate to check serum uric acid levels before initiating TMP/SMX therapy in patients with gout. If serum uric acid level is elevated, concomitant urate-lowering therapy may be renoprotective.
Liraglutide-Induced Hypercalcemia with AKI
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Introduction: Liraglutide is an approved agent for weight loss and to manage type 2 diabetes. We report a case of increased serum calcium with AKI in a patient treated with liraglutide.

Case Description: A 58-year-old Hispanic male with a history of hypertension, diabetes, and obesity was recently restarted on liraglutide by his primary care physician due to weight gain. He presented with myalgia, paresthesia, and fatigue. Physical exam was unremarkable except for a soft abdominal mass. Labs were notable for a serum calcium of 11.5 mg/dL (b/l 9.5-10.5 mg/dL), BUN 43 mg/dL, and creatinine 2.3 mg/dL (b/l 0.7-1.3 mg/dL). CT scan of abdomen showed a soft tissue density mass in the retroperitoneum measuring 8×7×7 cm, with increased vascularity. The patient was diagnosed with renal cell carcinoma and AKI was attributed to liraglutide.

Discussion: Our patient had a history of hypertension and diabetes, which are risk factors for hypercalcemia. Liraglutide, a GLP-1 agonist, can increase calcium absorption in the gastrointestinal tract. AKI in the setting of liraglutide is rare, but should be considered in patients with unexplained hypercalcemia in the setting of renal impairment.
mycotic pseudoaneurysm of the renal artery that resulted in subcapsular hematoma and Page kidney in an intravenous (IV) drug user.

**Case Description:** A 36-year-old female IV drug user presented with fever and hemoptysis. She denied history of kidney disease or preceding trauma. Admission blood pressure was 116/61 millimeter of mercury. Initial serum creatinine was 1.6 milligrams per deciliter (mg/dL). As noted, the patient had hypertension (160/70 mmHg). Renal ultrasound was unremarkable. She was found to have septic emboli on computed tomography (CT) of the chest, and methicillin-resistant Staphylococcus aureus (MRSA) grew in her blood cultures. Patient was diagnosed with infective endocarditis based on Duke’s criteria. She was started on IV antibiotics. On the third day of admission, she developed severe right flank pain and hematuria. She had worsening acute kidney injury and was started on hemodialysis. She was persistently hypertensive and progressively anemic. Hb dropped to 6.5 g/dL requiring transfusion of packed red cells. CT abdomen showed a new aneurysm and a large subcapsular hematoma of the right kidney. The bleeding pseudoaneurysm of the superior pole branch of the right renal artery was embolized by interventional radiology. She subsequently improved and no longer required hemodialysis. Plasma renin activity level returned elevated at 12.26 nanograms per milliliter per hour (reference 0.16-5.83).

Discussion: Renal artery aneurysm has a reported incidence of 0.1%. Subcapsular hematoma from rupture of mycotic pseudoaneurysm is a very rare complication of infective endocarditis. Page kidney is a hyperreninemic phenomenon that results from the renal ischemia secondary to external compressive forces from subcapsular hematoma. Elevated renin level and activation of the renin-angiotensin-aldosterone system usually occurs, as in our patient. For this reason, angiotensin converting enzyme inhibitors and relief of external compression are great treatment options in these patients.

PO0325

A Case of AKI with ANCA Vasculitis Associated Retroperitoneal Fibrosis

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**Introduction:** Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) refers to a group of multi-system autoimmune small vessel diseases that can give rise to a broad array of clinical signs and symptoms. ANCA-associated retroperitoneal fibrosis (RPF) is an exceptionally rare condition characterized by fibroinflammatory changes in the retroperitoneal space. Most RPF cases are idiopathic, or can be secondary to other medical conditions, the rarest association is with AAV. We present a case of ANCA-associated RPF in a patient with recurrent acute kidney injury (AKI).

**Case Description:** A 57-year-old male with a history of reactive arthritis presented to the hospital with acute left lower quadrant abdominal pain and found to have AKI due to obstruction by a soft tissue nodule on the left pelvic sidewall with mild-moderate hydronephrosis. He underwent left ureteral stent placement and his hydronephrosis resolved. Left iliac lymph node pathology was consistent with RPF. He was started on high-dose prednisone with resolution of his AKI. Steroids were tapered after repeat imaging 6 weeks later showed a decrease in the size of the soft-tissue nodule. He subsequently had a series of repeat admissions to the hospital with fevers, hypotension, shortness of breath, and recurrent AKIs. Each time, he was treated with antibiotics and stress-dose steroids with resolution of his symptoms. He was advised to return to the hospital as his symptoms progressed to include hemoptysis and etiopathosis. He was found to have proteinase-3 antibodies (PR-3) consistent with granulomatosis with polyangiitis and was started on rituximab.

**Discussion:** RPF in association with AAV is an extremely rare condition with very few cases documented in the literature. RPF is an uncommon collagen vascular disease characterized by inflammation of the retroperitoneal space which can produce obstruction notably affecting the abdominal aorta, iliac arteries and ureters. Mostly idiopathic, RPF can be associated with vasculitis, medications, infection, and neoplasms. As highlighted in this case, AAV should be considered with a recently diagnosed RPF and recurrent AKI. A hallmark is improvement of symptoms with steroids. This is important with reference to patient outcomes as delayed treatment, especially when renal disease is present, portends a higher risk of end stage renal disease and early mortality.

PO0326

Runaway Kidneys: First Case of Bilateral Herniated Kidneys in a Ventral Hernia

**Arecba Jawed, Samah S. Suleiman. Wayne State University School of Medicine, Detroit, MI.**

**Introduction:** Kidney herniation is extremely rare and typically seen in the setting of congenital defects. A handful of case reports have described traumatic thoracic herniation, postoperative renal transplant herniation and one report of postoperative incisional herniation. In this case report, we discuss the first case of bilateral kidney herniation into a ventral abdominal wall hernia.

**Case Description:** A 58-year-old male with a significant history of CKD stage IIIb hypertension, large abdominal wall hernia, hypothyroidism presented to the Emergency Department with complaints of abdominal pain and diarrhea. Vital signs were unremarkable. The physical exam was pertinent for morbid obesity (BMI 40kg/m2) and a non-reducible ventral hernia. Labs revealed serum creatinine of 4.77 mg/dL with a prior baseline of 1.9-1.8 mg/dL. CT scan without contrast showed a massive ventral hernia containing pancreas, bilateral kidneys and loops of bowel forming pannus overlying the right anterolateral pelvic wall. Persistent mild hydronephrosis without a definitive obstructive mass, obstruction might be caused by tethering of the proximal ureter to this large ventral hernia. No improvement in renal function was noted despite fluid resuscitation and Foley catheter placement. Urology was consulted and patient was taken for cystoscopy with bilateral retrograde pyelograms and left diverting single-J ureteral stent insertion. His renal function improved remarkably following relief of obstruction and serum creatinine down trended to 2.87mg/dL at discharge. Patient was scheduled to follow up with nephrology and urology at discharge.

**Discussion:** Kidney herniation is very uncommon and usually, only mobile structures, such as the small intestine and omentum are seen in ventral hernias. We postulate that mechanical forces related to obesity and prior surgeries played a role in the herniation of both kidneys which are normally firmly anchored in the retroperitoneum.
Acute kidney injury (AKI) is a disorder that is associated with high mortality and a high risk for development of chronic kidney disease. It is well documented that female gender is associated with relative resistance to kidney injury, the underlying mechanism is incompletely understood. Mounting evidence suggests that NAD + levels are associated with enhanced tolerance of kidney to injury, and exogenous supplement of NAD + precursor NMN alleviate AKI. The present study examined NAD + synthesis pathways and their association with gender related susceptibility to AKI.

Methods: IRI AKI model was performed on 8 weeks old wild-type C57BL/6J female and male mice, bilateral renal pedicles were clamped for 22 minutes. The animals were euthanized 48 hours after reperfusion. Prepubertal (3 weeks old) wild-type C57BL/6J and male mice, bilateral renal pedicles were clamped for 22 minutes. The animals were euthanized 48 hours after reperfusion, renin and aldosterone level were drawn measuring 3000 pg/ml (6 mo prior 1800) and 16 ng/dl (prior 12), respectively. Patient underwent renal artery duplex with noted bilateral RAS: ~60% diameter reductions and RI averaging 0.85. ACEI was promptly discontinued and within 48 hours, the patient’s Scr improved to 1.5, and he underwent CT-Angiogram (CTA) abdomen to determine if intervention needed. CTA noted bilateral moderate ostial RAS (left 50%, right 30%) due to progression of atherosclerotic calcifications. At follow up, yearly, BP and imaging remained stable, and he was recommended to see cardiology for closer monitoring.

Conclusions: In summary, while these data confirm the involvement of ferroptosis in spontaneous AKI, and identify β-estradiol as a general inhibitor of ferroptosis. This anti-ferroptotic effect explains the difference in sensitivity toward ATN of renal tubules of male and female mice.

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**PO0333**

**Distinct Spatiotemporal Dynamics of Damaged Proximal Tubular Epithelial Cells After Mild and Severe AKI in Mice**

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**Background:** Clinical and preclinical studies revealed that damage to proximal tubular (PT) epithelial cells after severe acute kidney injury (AKI) is a critical mechanism underlying the development of chronic kidney disease (CKD). Recent advancements of single-cell RNA sequencing (scRNA-seq) approach identified that PT cells adopt heterogeneous molecular states after injury and contribute to maladaptive repair. However, their fate after mild versus severe AKI remains poorly understood.

**Methods:** Single-cell transcriptomics and genetic fate-mapping approaches were used in our mouse model of unilateral ischemia-reperfusion injury (IRI) to investigate PT cell dynamics after short (20 min) and prolonged ischemia (30 min). For scRNA-seq analyses, we analyzed a total of 18,258 cells from the damaged kidneys harvested on 6 hours, and 1, 7, and 21 days after 30 min ischemia and the homeostatic normal kidneys. We used Seurat’s integration and label transfer to create the integrated dataset. To infer the dynamic cellular process during injury and repair, we used two computational tools (Monocle 3 and Velocyt).

**Results:** Our single-cell mouse atlas of maladaptive repair shows that PT cells develop a cell type clearly distinct, pro-inflammatory state following injury. These cells are characterized by reduced expression of homeostatic genes (ex. Lyp2, Slc3A4) and enrichment of genes associated with kidney development (ex. Sox9, Cdhh6) and kidney injury (ex. Fcml1, Hacre1). Gene ontology analysis of these cells revealed high enrichment for pro-apoptotic signaling. Our genetic fate-mapping using a Sox9CreERT2; Rosa26-atdTomato mouse line showed these inflammatory PT cells transiently appear after short ischemia and return to their original state without inducing fibrosis. However, they accumulate and contribute to persistent inflammation after prolonged ischemia.

**Conclusions:** Our single-cell transcriptomic and genetic fate-mapping approaches identify that the accumulation of inflammatory PT cells after severe injury underlies the maladaptive repair process. Future studies of how this pathologic cell state persists and contributes to inflammation will inform us to develop novel therapeutic approaches for AKI and its transition to CKD.

**Funding:** NIDDK Support, Private Foundation Support

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**PO0335**

**Cell Interaction Dynamics in Human AKI Revealed by Single-Cell Transcriptomics**

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**Background:** Single cell transcriptomic maps of human AKI have not been reported, in part due to the difficulty of obtaining tissue. Acute kidney injury (AKI) is characterized by dynamic changes in cellular interactions among epithelia, stroma and inflammatory cells across the acute injury, repair and failed repair spectrums. Single cell transcriptomic technology is ideally suited to unravel the spectrum of cell states and interactions during injury and repair.

**Methods:** We performed snRNA-seq on 4 human AKI samples (2M and 2F, mean age = 60y, mean sCr = 4.6 mg/dl) and 5 control samples (3M and 2F, mean age = 55.8y, mean sCr = 1.07 mg/dl). Nuclear preparations were processed using 10x Genomics v3 v3 Chromium kits and sequenced by NovaSeq. Reads were counted with CellRanger and analyzed with Seurat.

**Results:** After quality control and doublet removal, 62,649 nuclei (18 clusters) were identified in the dataset. G1L1 expressing fibroblasts were enriched in AKI, suggesting hedgehog signaling pathway activation. Among ligands, DHH expression was specifically up-regulated in the ADAMTS6*-endothelial subset in AKI, suggesting that AKI-induced endothelial stress may activate fibroblast reprogramming for myofibroblast proliferation. Comprehensive ligand-receptor analysis suggests secreted proteins including TRAIL and DHH dependent intercellular signaling. We define the transcriptomic signature of failed-repair PT in human AKI and show that this is similar to that of primary cultured RPTEC, validating primary RPTEC as a model of failed repair. Indeed, TNFα treatment of RPTEC drove expression of the full complement of failed repair PT marker genes, suggesting a critical role for NFkB activation in human PT injury and repair.

**Conclusions:** This is the first single cell transcriptomic atlas of human AKI. It reveals a novel PT-endothelium-myofibroblast signaling loop coupling PT injury to endothelial stress and ultimately interstitial fibrosis. This TRAIL and DHH dependent intercellular signaling cascade suggests a molecular mechanism for the AKI to CKD transition.

**Funding:** NIDDK Support

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**PO0337**

**Distinct Spatiotemporal Dynamics of Damaged Proximal Tubular Epithelial Cells After Mild and Severe AKI in Mice**

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**Background:** Human acute kidney injury (AKI) is a multifactorial process and severity varies between individuals. The murine cisplatin model is a replicable example of AKI with limited confounding variables. We determined the pathways and injury markers dysregulated across the nephron in cisplatin AKI. We localized relevant human cell state signatures with spatial transcriptomics (ST) to determine which were most prevalent in cisplatin AKI and where these cells reside.

**Methods:** Six 129S6-SVE mice received vehicle or cisplatin (0.5 mg/g). After 72 hours, mouse kidneys were harvested and preserved for histology, single cell sequencing (scRNAseq), and ST. Gene mapping was completed with Cell Ranger 5.0.1 (scRNAseq) or Space Ranger 1.2.0 (ST). Human scRNAseq data was downloaded from kpmp.org, clustered by cell state (injured, adaptive, degenerative, transitioning, cycling, or reference) and mapped to mouse orthologs in Enembl database. Seurat clustered and integrated scRNAseq data as well as performed spatial mapping. Visualizations were created with R Studio.

**Results:** Cisplatin mice had increased BUN and tubular atrophy. scRNAseq identified 32 cell clusters, merged across common cell types. Cell cycle genes (Cdkn1a) were upregulated across epithelial cell types, but injury markers (Lcn2 and Spp1) were on space Ranger 1.2.0 (ST). Human scRNAseq data was downloaded from kpmp.org, clustered by cell state (injured, adaptive, degenerative, transitioning, cycling, or reference) and merged across common cell types. Cell cycle genes (Cdkn1a) were identified and defined by cell cycle markers, Lcn2 and Spp1, suggesting a distal nephron origin despite dedifferentiation. Cdkn1a was upregulated in ST across all cell types, but the novel injury cluster mapped only to the outer renal cortex. From the 6 identified human cell states, the adaptive epithelial state was found to be upregulated in cisplatin mice.

**Conclusions:** This study localizes the differential effects of cisplatin across the nephron. It adds support to the human injury cell states defined from scRNAseq of heterogenous human samples, showing their relevance in a well-defined AKI model.
Unraveling Single-Cell Responses in Human AKI

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Background: Acute kidney injury (AKI) is frequently observed in critically ill patients and is associated with a poor prognosis. AKI has recently moved into the focus of interest during the SARS-CoV-2 pandemic as high rates of AKI have been reported in severe COVID-19. We aimed to delineate cell type-specific molecular phenomena associated with human AKI, including COVID-associated AKI.

Methods: We analyzed human kidney tissue histology and single-nucleus RNA sequencing. Samples included kidney biopsies obtained within 2 hours post mortem from patients who succumbed to critical illness with and without evidence of AKI. Samples also included tumor-adjacent normal kidney tissues obtained during surgeries. AKI cases included patients with severe courses of COVID-19 (COVID-AKI) and patients with other critical illness associated with systemic inflammation (Non-COVID-AKI). Post-mortem kidney tissues obtained 30 min, 1 hour and 2 hours after death from a brain-dead patient without AKI were analyzed to assess the impact of post-mortem effects.

Results: Single-nucleus sequencing from kidney tissues yielded data of high transcriptional depth, which allowed transcriptome-based identification and de-novo spatial reconstruction of kidney cells. Principal component and differential gene expression analyses indicated that the presence of clinically confirmed AKI was the primary driver of global kidney transcriptomes and that different molecular subtypes of AKI existed. In contrast, the sampling time post-mortem and the presence of COVID-19 had minor effects. Subclustering analyses of different kidney cell types identified subclasses of cells representing injured kidney tubular cells, which were marked by distinct biomarker expression and expression signatures signifying intrinsic responses to inflammation, an induction of epithelial-to-mesenchymal transition, and an upregulation of hitherto unrecognized novel receptor-ligand pairs.

Conclusions: We provide the first cell type-specific molecular atlas of human AKI, revealing unanticipated disease subtypes and cell type-specific injury patterns.

Mechanisms of Nucleophosmin-Mediated Regulated Cell Death During Renal Ischemia

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Background: Nucleophosmin (NPM) is a protein chaperone that potentiates Bax-mediated cell death during ischemic AKI by an unknown mechanism. In contrast, heat shock protein 70 (Hsp70) is a potent anti-apoptotic agent that promotes renal cell survival and preserves organ function. In this study, we characterize for the first time the intracellular events in which NPM and Hsp70 compete to regulate cell survival during ischemic stress.

Methods: Hsp70 wild type (WT) or Hsp70 mutants either restricted to the cytosol (Hsp70 985A) or unable to enter the nuclear region (Hsp70 M45) were selectively over-expressed in primary murine proximal tubule epithelial cells (PTEC) harvested from Hsp70 null mice. Hsp70 expression, NPM nuclear translocation, NPM de-oligomerization, NPM-Bax complex formation, T95 phosphorylation responsible for NPM translocation, and cell survival were measured.

Results: Equivalent, selective over-expression of the hsp70 proteins significantly improved cell survival after ischemia stress in the following rank order: WT > M45 > 985A (each P < 0.05 vs. control). Only Hsp70 members with nuclear access (WT and M45) inhibited T95 phosphorylation that mediates NPM translocation and reduced cytosolic NPM accumulation. Neither WT nor the Hsp70 mutants inhibited stress-induced NPM de-oligomerization. In contrast, WT > 985A > M45 Hsp70 significantly improved survival in Hsp70 null PTEC that expressed a cytosol-restricted NPM mutant, interacted with cytosolic NPM, and reduced NPM-Bax complex formation required for mitochondrial injury and cell death. Hsp70 knockout prevented the cytoprotective effect of suppressing NPM in ischemic PTEC and also increased cytosolic NPM accumulation after acute renal ischemia in vivo, emphasizing the protective effects of Hsp70 on NPM-mediated renal cell toxicity.

Conclusions: These observations identify key steps that mediate NPM toxicity during ischemia-induced cell death: (1) nuclear NPM de-oligomerization, (2) NPM translocation into the cytosol and (3) cytosolic NPM-Bax complex formation. Hsp70 promotes renal cell survival during ischemic acute kidney injury partly by inhibiting two of these toxic events in distinct cell compartments: nuclear NPM translocation and NPM-Bax interaction in the cytosol. Renal cell survival during ischemic AKI is substantially improved by interfering with events that render NPM toxic.

Funding: NIDDK Support

Limonin Protects Against AKI by Targeting ERK Signaling

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Background: Acute kidney injury (AKI) is characterized by tubular cell injury, vascular dysfunction, and inflammation. As a key pathological event, sustained inflammation in AKI plays a critical role in accelerating disease progression. In the clinic, there are no effective therapeutic strategies to prevent AKI by thus far. We previously reported, Limonin, a member of the class of compounds known as furanolactones possesses potent anti-inflammatory effects in multiple immuno-diseases. Whether Limonin could serve as a candidate to preserve renal function after AKI remains unclear.

Funding: Government Support - Non-U.S.
Methods: Kidney ischemia-reperfusion injury (IRI) was employed to induce AKI in mice. After two days before IRI, a molecular docking study and thermal shift assays were performed to determine the binding capacity between Limonin and key targets. In vivo and in vitro molecular experimental pathology studies were applied. Results: After ischemic AKI, pretreatment of Limonin preserved kidney functions, ameliorated tubular injury, and repressed inflammation in the diseased kidneys, compared to the vehicle. In our model, Limonin has active binding sites for 38 significant target proteins, including ERK. A molecular docking study demonstrated a high binding affinity between Limonin and ERK2, and Limonin, which was confirmed by the temperature- and dose-dependent cellular thermal shift assays. In vivo, we further revealed that Limonin activated ERK signaling pathway and then promoted tubular cell proliferation and reduced cell apoptosis after AKI. In vitro, blockade of ERK signaling abolished the abilities of Limonin in protecting tubular cell apoptosis under hypoxia conditions.

Conclusions: Our results indicated that Limonin is a novel ERK activator. Its therapeutic effect on murine AKI paved a new avenue for AKI intervention in the clinic.

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PO0341
Inhibition of miR-155 Ameliorates AKI by Protecting Telomeres and Reducing DNA Damage of Renal Tubular Cells

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Background: Acute kidney injury (AKI) is associated with significant morbidity and mortality, and currently there is no therapy to prevent or treat established AKI. miR-155 is significantly up-regulated in diabetic nephropathy, IgA nephropathy, bilateral renal ischemia-reperfusion injury (IRI) or drug-induced AKI. However, the molecular mechanism of miR-155 in AKI remains to be studied.

Methods: We subjected miR-155−/− mice and wild-type controls, as well as human proximal tubule cells, to cisplatin-induced AKI models. We assessed kidney function and injury with standard techniques and measured telomere by the fluorescence in situ hybridization.

Results: The expression level of miR-155 was upregulated in both cisplatin-induced AKI mice model and cisplatin-treated HK2 cells. Inhibition of miR-155 expression protected cisplatin-induced AKI both in vivo and in vitro. Compared with wild-type mice, miR-155−/− mice had reduced mortality, improved renal function and pathological damage after cisplatin intervention. Moreover, inhibition of miR-155 expression decreased cells apoptosis and suppressed DNA damage. Additionally, we found that miR-155 efficiently regulates TFI expression by targeting a partially conserved sequence motif in the TFI 3’UTR. Inhibition of miR-155 enhanced the expression of TFI and reduced the telomere DNA damage induced by cisplatin. In addition, CDK12 had also been identified as a novel target of miR-155. Inhibition of miR-155 increased the expression of CDK12, and reduced DNA damage and mRNA and telomere stability.

Conclusions: We demonstrated that inhibition of miR-155 ameliorates AKI involving the targeting and regulation of TFI and CDK12, indicating a novel regulatory mechanism and elucidating a potential target for cisplatin induced AKI treatment.

Funding: Government Support - Non-U.S.

PO0342
Evaluation of Urinary NHE3 in Rats with AKI

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Background: Acute kidney injuries (AKIs), caused by hypoxemia, ischemia-reperfusion, or nephrotoxins, are concerned with high morbidity and mortality. Urinary Nai-H exchanger isoform 3 (NHE3) has been demonstrated as a noninvasive marker of acute tubular necrosis. However, the ideal diagnostic biomarker in AKI is still lacking.

Methods: In order to determine the potential role of urinary NHE3 in early diagnosis of AKI, we evaluated the expression of NHE3 in daily urines from rats models of AKI including low NaCl (0.1%) plus candesartan (1mg/kg/day, IP) for 7 days, ischemia-reperfusion (ischemia for 40 min, reperfusion for 2 h) and cisplatin (20mg/kg for 7 days) in Sprague Dawley rats (male, 2-3 months old, 4-7 rats per group). Urine NHE3 was isolated by a series of centrifuges including ultracentrifuges (17,000 g, 4°C, 1min; 20,000 g, 4°C, 1 h).

Results: NHE3 levels (western blotting) were increased at day 1, which was 1 day before serum creatinine increased in low NaCl/candesartan rats and reperfusion rats (day 1) relative to controls. They were also increased in cisplatin rats at day 2 (1 day before serum creatinine increased). Furthermore, NHE3 in original urines from 6 patients diagnosed with AKI (Scr 249.8±166.93 umol/L) and 6 volunteers with normal renal function (Scr 68.6±13.20umol/L) were assessed without ultracentrifuge isolation. NHE3 was increased remarkably in AKI patients (333±28, % of controls) compared with controls (100±30, %, P<0.05).

Conclusions: Our results in rats and patients suggest that assessment of urine NHE3 may be a potential non-invasive biomarker for early detection of various acute kidney injuries.

Funding: Government Support - Non-U.S.

PO0343
TBα-Catenin Ameliorates AKI by Restoring Mitochondrial Biogenesis

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Background: Renal tubular β-catenin signaling plays a protective role in acute kidney injury (AKI), but the underlying mechanisms remain unclear. Mitochondrial dysfunction is responsible for the pathogenesis of AKI. This study aims to investigate the role of β-catenin activation on mitochondrial biogenesis in tubular cells upon AKI and its underlying mechanisms.

Methods: Loss- and gain-of-β-catenin function was established in mice with tubular cell-specific β-catenin stabilization (TubCat mice) and knockout (TubCatKO mice). Septic and septic and aseptic AKI were induced by exposure to LPS or ischemia/reperfusion, respectively. Kidney injury was examined by NGAL immunohistochemical staining. Markers of mitochondrial biogenesis were determined by Western blot, real-time quantitative PCR and immunofluorescence staining. Signaling cascade was examined by Western blot.

Results: Compared to the controls, TubCat mice under septic and aseptic AKI had significantly increased kidney and bladder mitochondria biogenesis as indicated by (i) reduction of NGAL positive tubules; (ii) restoration of mitochondrial mass protein TOMM20 and mitochondrial biogenesis molecules PGC-1α and NRF1; (iii) increasing co-localization of PGC-1α and β-catenin in renal tubules and (iv) increasing FOXO3 signal to septic and aseptic injury. Consistently, kidney injury, and mitochondrial dysfunction were aggravated in TubCatKO mice versus their control littermates.

Conclusions: In both septic and aseptic AKI, tubular β-catenin stabilization restores mitochondrial homeostasis through the FOXO3/PGC-1α signaling pathway.

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PO0344
CB11: Mitochondrial Effects in Renal Proximal Tubular Cells

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Background: Oxidative stress and mitochondrial dysfunction are characteristic of many acute and chronic conditions such as acute kidney injury and chronic kidney disease. Renal proximal tubular cells (RPTC) are mitochondria-dense, dependent on oxidative phosphorylation, and are particularly susceptible to injury. Identifying compounds that induce mitochondrial biogenesis (MB) is of increasing importance for the treatment of renal diseases associated with metabolic dysfunction. We investigated the effects of 1-butyl-3-hydroxy-1H-2-[2-oxo-2-(pyridin-2-yl)ethyl]-1,3-dihydro-2H-indol-2-one, (CB11), on MB, mitochondrial dynamics, antioxidant response, and apoptosis in RPTC using a model of sodium-induced injury in some NHE3−/− mice.

Methods: In primary cultures of renal proximal tubular cells, we used uncoupled oxygen consumption rate (FCCP-OCR), transmission electron microscopy, immunoblotting, oxidant-induced injury with tert-buty1 hydroperoxide (TBHP), and flow cytometry.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: CB11 (0.1 mg) treatment increased FCCP-OCR and mitochondria number after 24 h pretreatment. CB11 exposure decreased expression of fusion protein Mfn1 at 1 and 10 nM concentrations. CB11 had no effect on fusion proteins Mfn2 or OPA1 or phosphorylation of fission protein Drp1 at serine residues 637 or 616. Expression of Nrf2 protein decreased with no effect on Nrf2-regulated antioxidant response proteins (e.g. NQO1, GSTT1). Following a 24 h pretreatment with CB11, TBHP-induced injury was decreased at 1 h evaluated. CB11 exposure did not prevent the loss of monolayer confluence at 1h post-injury. However, daily exposure prevented further loss of confluence at 48, 72, and 96h. No significant change in apoptosis, as measured by annexin-V positive cells (AnnV+), was noted in I/R mice and was restored to control levels in I/R+lasmiditan group. The tight junction proteins occludin, ZO-1, and Claudin 5 decreased in the I/R+vehicle group and was restored to control levels in the I/R+lasmiditan group. The tight junction proteins PGC-1α and electron transport chain complexes IV and V were restored in I/R+lasmiditan group and was restored to control levels in the I/R+lasmiditan group.

Conclusions: CB11 represents a new and highly potent inducer of MB with a unique signaling pathway in RPTC. Our data reveal that CB11 pretreatment does not prevent occludin decreased cell but acts as a RPTC protectant. Future studies will test this compound in AKI and CKD models.

Funding: Commercial Support - University of Arizona

PO0345

FDA-Approved Drug Lasmiditan Stimulates Mitochondrial Biogenesis and Promotes Recovery of Vasculature and Renal Function After Ischemia-Reperfusion Injury in Mice

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Background: Acute kidney injury (AKI) is induced by multiple mechanisms (e.g. ischemia/reperfusion (I/R), drugs, sepsis) and results in tubular and vascular dysfunction. Mitochondrial function is a key mediator of injury and recent studies have shown that pharmacological-induced mitochondrial biogenesis (MB) can provide renal recovery. Activation of the 5-HT1F receptor has been demonstrated to induce MB in the mouse kidney and the absence of said receptor results in greater renal injury from I/R, demonstrating the importance of the 5-HT1F receptor in the kidney. The goal of this study was to test the efficacy of the potent, selective, and FDA-approved 5-HT1F receptor agonist lasmiditan in a mouse I/R-induced AKI model.

Methods: Male mice were subjected to I/R-induced AKI. After 24 h, serum creatinine was measured and I/R mice were divided into two groups and dosed with lasmiditan (0.3 mg/kg) or vehicle. Daily dosing was continued until euthanasia at 144 h. Electron microscopy was used to measure mitochondrial number. Serum creatinine was measured. Vascular leakage was determined using Evan’s blue dye and tight junction proteins were measured using immunofluorescence microscopy.

Results: CRE and mitochondrial number in I/R+lasmiditan group. The tight junction proteins PGC-1α and electron transport chain complexes IV and V were restored in I/R+lasmiditan group and was restored to control levels in the I/R+lasmiditan group.

Conclusions: In this study we demonstrate that FDA approved lasmiditan restores mitochondrial function and renal and vascular function after I/R injury in mice. Lasmiditan could be repurposed for the treatment of AKI in humans.

Funding: Veterans Affairs Support

PO0346

Treprostinil Improves Mitochondrial Dynamics and Reduces Oxidative Stress During Renal Ischemia-Reperfusion Injury in Rats

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Background: Renal ischemia-reperfusion injury (IRI) is a major factor that contributes to acute kidney injury (AKI). Mitochondria enriched in renal proximal tubular cells are particularly susceptible to IRI-induced oxidative stress. Currently, there is no treatment for IRI available. We recently demonstrated the efficacy of treprostinil (Rastem) in reducing AKI dynamics and improving renal IRI. This study investigates the role of treprostinil in improving mitochondrial dynamics and reducing oxidative stress during renal IRI.

Methods: Male Sprague Dawley rats were subjected to 45 minutes of bilateral renal ischemia and then 24 h of reperfusion. A treprostinil dose dependent effect on reducing AKI dynamics and improving renal IRI was observed. A treprostinil dose response effect was observed in mitochondrial levels.

Results: Treprostinil significantly reduced renal injury and peak elevated serum creatinine, GFR, and I/R injury was decreased in the I/R+lasmiditan group compared to I/R+vehicle group. A treprostinil dose response effect was observed in mitochondrial levels. A treprostinil dose response effect was observed in mitochondrial levels.

Conclusions: In this study we demonstrate that FDA approved lasmiditan restores mitochondrial function and renal and vascular function after I/R injury in mice. Lasmiditan could be repurposed for the treatment of AKI in humans.

Funding: Veterans Affairs Support

PO0347

Regulation of Mitochondrial Metabolism in T-Regulatory Cells by Programmed Cell Death Protein 1 in AKI

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Background: The T-regulatory cells (Tregs) are important for suppressing inflammation and for resolution of injury during acute kidney injury (AKI). Absence or inhibition of programmed cell death protein 1 (PD-1) mitigates the Treg-mediated protection in AKI. The mechanisms, however remain unknown. Here we test the hypothesis that PD-1 regulates mitochondrial metabolism of Tregs during AKI.

Methods: In vivo and in vitro experiments were performed to examine the role of PD-1 in regulating mitochondrial metabolism of Tregs during AKI.

Results: In vivo and in vitro experiments were performed to examine the role of PD-1 in regulating mitochondrial metabolism of Tregs during AKI.

Conclusions: Programmed cell death protein 1 (PD-1) regulates mitochondrial metabolism of Tregs during AKI.

PO0348

Regulation of Mitochondrial Cardiolipin Targeting Peptide Ameliorates Kidney Oxidative Damage

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Background: Mitochrondria is a major organelle of adenosine triphosphate production and O2 consumption. Also, kidney is mitochondria abundant organ. Many mitochondria-targeting agents were developed, though there is no single agent approved in clinical practice. We investigate renoprotective effect of newly invented mitochondrial cardiolipin targeting peptide, the SNU-RD, in hypoxic condition.

Methods: Based on our experience that dimer formation by bisulfate bond of cell penetrating peptide accelerate permeability, we synthesized 15 candidate tetra-peptides which target inner mitochondrial membrane specific phospholipid, the cardiolipin. After cell viability, distribution and mitochondrial functional test, we selected best candidate and tentatively named as SNU-RD. As hypoxic damage, bilateral ischemia-reperfusion injury (IRI) and primary cultured human proximal tubular epithelial cells (pTECs) with H2O2 were chosen. Wild-type mice were divided into four groups: sham, IRI, IRI with low dose or high dose SNU-RD. After SNU-RD treatment with various concentration (10nM, 100nM, 1000nM), high dose H2O2 stress was done. Mitochondrial function was tested and mitochondrial oxygen consumption rate (OCR) was measured.

Results: In IRI, renal BUN and creatinine were significantly decreased without SNU-RD dose dependency. Pathologic findings (NGAL and cytchrome C) were improved. Also, mitochondrial anti-oxidative enzyme (NQO-1, SOD-1), ATP6 and IL-10 mRNAs were over-expressed after SNU-RD treatment. Cell viability was increased with dose dependently decrease of early apoptosis. IL-1β, IL-18, p16 and p31 mRNA were dramatically down-regulated. When traced by rhodamine, SNU-RD was intensively distributed to mitochondria then cytospin. In JC-1 assay, ratio of healthy mitochondria was increased with SNU-RD. Basal and maximal OCR were much recovered from SNU-RD (10nM).

Conclusions: Mitochondrial cardiolipin targeting peptide, SNU-RD can protect kidney from hypoxic injury by restoring mitochondrial function.
metabolism of isolated Tregs was assessed ex vivo using Seahorse Metabolic Flux Analyzer and staining with mitochondrial membrane potential and ROS production respectively, as well as by RT-PCR for genes related to mitochondrial dynamics. Scanning Electron microscopy (SEM) was performed on isolated Tregs to image mitochondrial morphology followed by ImageJ™ analyses. Using SEM and ImageJ™, the mitochondria in Tregs from PD-1-/- mice were fewer in number and had lower average pixel area. Conclusion: The data suggest that PD-1 regulates mitochondrial function and dynamics of Tregs and this is critical for protection from AKI and other inflammatory diseases. Funding: NIDDK Support

**PO0349**

Intrflagellar Transport Protein 88 Deficiency in Proximal Tubular Cells Exaggerates Cisplatin-Induced Injury by Suppressing Autophagy

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Background: Primary cilia are widely regarded as specialized sensors in differentiated cells that have been implicated in the regulation of cell proliferation, differentiation, and survival. We previously showed that shortening of primary cilia sensitizes cultured kidney tubular cells to cisplatin-induced apoptosis. IFT88 is an essential component for ciliogenesis and maintenance.

Methods: To study the effect of proximal tubule-specific IFT88 ablation on cisplatin-induced kidney injury (AKI), we took advantage of conditional IFT88 knockout mice to study how differently cisplatin affected renal function in knockout mice and age- and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

Results: It was found that more severe AKI occurred in IFT88 knockout mouse than controls. Mechanistically, cisplatin stimulated autophagy in kidney tubular cells as an intrinsic protective mechanism. However, renal autophagy was severely impaired in IFT88 knockout mouse. In cultured HK-2 cells, cisplatin induced more apoptosis when IFT88 was knocked down. TAT-becn1 peptide, a specific autophagy activator, could partially prevent IFT88-associated cell death during cisplatin treatment, although citium length was not improved significantly.

Conclusions: These results indicate that defective autophagy in IFT88-deficient kidney cells and tissues contributes to the exaggerated AKI following cisplatin exposure. Funding: NIDDK Support, Veterans Affairs Support

**PO0350**

Urinary UDP-Glucose as a Novel Actionable Biomarker of Dehydration-Induced AKI

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Background: People working in "extreme" conditions such as sugar cane workers, firefighters, and military personnel are subjected to significant dehydration. Prolonged episodes of dehydration may result in acute kidney injury (AKI). AKI is associated with high mortality and is usually diagnosed only after the kidneys have gone through significant and often irreversible damage. We showed that the P2Y14 receptor mediates renal inflammation leading to AKI following ischemia-reperfusion injury. P2Y14 is activated by the danger molecule UDP-glucose (UDP-Glc). Here we hypothesized that UDG-Glc is released by damaged cells throughout the body after dehydration-induced stress. UDG-Glc is filtered by the kidney and concentrated in collecting ducts where it activates P2Y14 in intercalated cells. This would trigger renal inflammation and contribute to dehydration-associated AKI.

Methods: To study the effect of water deprivation for 24, 48 and 72 hours. Kidney function was assessed by serum creatinine (Scr), blood urea nitrogen (BUN) and urine albumin. To study proximal tubule (PT) damage, aquaporin 1 (AQP1) localization was analyzed by immunofluorescence (IF). Urinary UDG-Glc concentration was measured by LC-MS/MS. Results: Contrary to the WT, adaptive transfer of PD-1-/- Tregs was unable to protect the recipient mice from IRI-induced AKI. The oxygen consumption rate (OCR), a measure of oxidative phosphorylation, was significantly reduced in PD-1-/- Tregs at baseline and under maximal respiration as compared to WT. PD-1-/- Tregs also had reduced mitochondrial mass, lower mitochondrial membrane potential, and reduced mitochondrial ROS production than WT Tregs. Further, the expression of Pgc1a, Nrf1, Brf2, Tfam, Drp1, Mfn1, Mfn2 and Mff was also significantly reduced in the PD-1-/- Tregs. Importantly, compared to Tregs from age and sex-matched WT mice and as measured using a mH2B and mCherry reporter, the mitochondria in Tregs from PD-1-/- mice were fewer in number and had lower average pixel area.

Conclusions: The data suggest that PD-1 regulates mitochondrial function and dynamics of Tregs and this is critical for protection from AKI and other inflammatory diseases. Funding: NIDDK Support

**PO0351**

Role of Collagen Receptors in Radiation-Induced Nephrotoxicity

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Background: Radiation therapy represents a severe late complication for cancer patients that induces radiation nephropathy (RN). Collagen receptors (CD44, discoidin domain receptor 1 (DDR1) and integrin α2) are involved in the pathogenesis of renal fibrosis. However, the mechanisms is largely unknown. We hypothesized that radiation therapy (RT)-induced collagen 1 accumulation in podocytes activates DDR1, integrin α2, and matrix metalloproteinases (MMPs) signaling leading to changes in the laminin and collagen homeostasis in GBM thus inducing RN.

Methods: 10–14-weeks old C57BL/6 male and female mice received a single dose (SD) 40g, 10g, and 4gY or fractionated dose (FD) 60gYs and 20gys x24 irradiations. Kidney function parameters (estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), serum BUN and creatinine), histopathological changes (determined by H&E, Periodic Acid-Schiff (PAS), Picrosirius red (PSR)), gene expression analysis (by nanoliter), ultrastructural changes by transmission electron microscopy (TEM), were measured at 10- and 20-weeks post-SD and FD.

Results: IHC and nanostringning showed a significant upregulation of Col I, pDDR1, and integrin α2 expression (p<0.001) and reduction in integrin α1 (p=0.001) in kidney cortices 10 and 20 weeks post-SD and FD. Western blot and gene expression analysis showed that several MMPs expression increased significantly in a dose- and time-dependent manner in cultured human podocytes and mouse kidney cortex post-RT. Significant reductions were seen in collagen type IV (Col4A3, Col4A4, Col4A5), laminin α5β1γ1 (LM-521) and a substantial increase in the expression of collagen type I (Col1A1, Col1A2, Col1B1) and collagen type III (Col3A1) in radiated mice kidney cortex (p<0.001). TEM data demonstrated time and dose-dependent increases in GBM thickness and foot process width (p<0.001). Significant increases in fibrosis (PSR), mesangial expansion (PAS), ACR in association with collagen deposition were observed 20 weeks post 40gY and 20-weeks post FD was observed.

Conclusions: Our data suggest that targeting collagen receptors (DDR1 and integrin α2) with specific small molecule inhibitors genetic and pharmacological induction of integrin α3 may prevent the RN. Funding: Other NIH Support - NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002647 and National Institute of Health Funding - Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002647 and National Institute of Health funding.

**PO0352**

Leucine Metabolism and Ketone Bodies Role in AKI

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Background: Renal ischemia reperfusion (IR) results in injury caused by dynamic process that includes inflammation and extensive cell death. The increase in oxidative stress appears to play a great role in the inflammatory process causing acute kidney injury (AKI) during IR. Oxidative stress activates p53 and promotes cell death. On the other hand, ketones, produced in the liver from fatty acids, are oxidized in the liver and released into the blood. In this study, we investigate the role of ketones in AKI. We hypothesized that ketones are renal protective under different pathological conditions including AKI. Acetoacetate, one of the major ketones bodies, is a product of leucine catabolism. The means through which ketone bodies could play a protective role still requires further understanding. Computational studies in our lab have uncovered a link between mouse double minute 2 homolog (MDM2), which is a direct inhibitor of p53, and methylcrotonyl-CoA carboxylase 2 (MCC2), which encodes a mitochondrial enzyme essential for leucine and isovaleric acid catabolism.

Methods: To explore amino acid metabolism and ketone bodies role in AKI we analyzed gene expressions in kidney cortex of mice that have undergone 35 minutes of renal ischemia followed by 24h of reperfusion. Moreover, to further investigate a connection between MDM2 and MCC2, we knocked-down MDM2 in human kidney 2 (HK2) cells using small interfering RNA (siRNA) transfection at 2 concentrations (100nM and 200nM). Cells were harvested 48 hours post-transfection for mRNA and protein analysis.

Results: Renal ischemia-reperfusion increased levels of p53 and HIF1-α alpha consistently with previous studies. Intriguingly, we also got significant decrease in leucine (Leu) and isoleucine (Ile) (n=6) in HK2 cells compared to sham operated. In HK2 cells, the relative increase in protein expression of p53 and HIF1-α alpha is observed.

Conclusions: Though preliminary, our data show a consistent decrease in MDM2 expression at the mRNA levels under AKI provoked by IR. This novel finding could be a steppingstone towards deciphering important pathways in AKI that involve oxidative stress related cell death and dysregulated amino acid metabolism. Funding: Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002647 and National Institute of Health funding.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0353
Targeting Polycomb Repressive Complex 2 Protects Against Cisplatin-Induced AKI in Mice
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Background: Our previous studies have shown that blocking EZH2 (Enhancer of Zeste Homolog 2), a catalytic subunit of polycomb repression complex 2 (PRC2) with histone methyltransferase activity, protects against acute kidney injury (AKI). The role and mechanism of the entire PRC2 in AKI remain undefined. In this study, we investigated the involvement of PRC2 in the pathogenesis of AKI following cisplatin exposure.

Methods: A potent and selective PRC2 inhibitor EED226 was used to evaluate the effect of loss of PRC2 catalytic activity on renal function and tubular cell injury as well as activation of key apoptotic signaling pathways and expression of renoprotective proteins in a murine model of cisplatin-induced AKI.

Results: Administration of EED226 improved renal function, attenuated renal pathological changes, and reduced renal tubule injury and apoptosis in a murine model of cisplatin-induced AKI. In cultured renal epithelial cells, treatment with either EED226 or EED siRNA also reduced apoptosis. Mechanistically, EED226 treatment inhibited cisplatin-induced phosphorylation of p53 and fox3a, two transcriptional factors associated with apoptosis, and prevented downregulation of expression of Sirt3 and PGC-1α, two proteins that contribute to mitochondrial protection. Moreover, EED226 also enhanced renal tubular cell proliferation and suppressed inflammatory responses and phosphorylation of STAT3 and NF-kB, two transcriptional factors associated with inflammation.

Conclusions: These results indicate that targeted inhibition of PRC2 can improve renal function and promote the survival and proliferation of renal tubular cells through mechanisms associated with inhibition of p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α.

Funding: Government Support - Non-U.S.

PO0354
Kidney Protection by Caloric Restriction Depends on De Novo NAD+ Synthesis Activation
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Background: In clinical practice, targeted treatments for the measure of acute kidney injury (AKI) are lacking. In mouse models, AKI by ischemia-reperfusion injury (IRI) can be protected by caloric restriction protocols using hypoxia (HP) or caloric restriction (CR). In previous transcriptome analyses of murine kidneys after HP or CR, we identified Kynu as one of the key enzymes in tryptophan metabolism and the aim of this work was to further characterize the role of Kynu in the protection of AKI.

Methods: CRISPR-cas9 based non-homologous end joining (NHEJ) resulted in a Kynu-deficiency in C57Bl6 mice. This was followed by basal (e.g. biometry, kidney function) and special (e.g. kidney function 24h after renal IRI with or without HP/CR) phenotypeing of the Kynu-deficient (KYNUnull) mice in comparison to wildtype (KYNUwt) mice. In cultured renal epithelial cells, treatment with either EED226 or EED siRNA also reduced apoptosis. Mechanistically, EED226 treatment inhibited cisplatin-induced phosphorylation of p53 and fox3a, two transcriptional factors associated with apoptosis, and prevented downregulation of expression of Sirt3 and PGC-1α, two proteins that contribute to mitochondrial protection. Moreover, EED226 also enhanced renal tubular cell proliferation and suppressed inflammatory responses and phosphorylation of STAT3 and NF-kB, two transcriptional factors associated with inflammation.

Conclusions: These results indicate that targeted inhibition of PRC2 can improve renal function and promote the survival and proliferation of renal tubular cells through mechanisms associated with inhibition of p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α.

Funding: Government Support - Non-U.S.

PO0356
Lack of Gb3 Elevated Renal Tubular Injury in a Mouse Model of Aristolochic Acid Nephropathy
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Background: Globotriaosylceramide (Gb3) is a glycosphingolipid serving as the receptor for Shiga toxin (Stx) and is responsible for mediating binding of Stx onto kidney tissues. However, the normal physiological function of Gb3 in kidney remains unknown. Under normal circumstances, Gb3-knockout (KO) mice (A4GALT+/-, 4-galactosyltransferase) showed no obvious physical and chemical abnormalities. Gb3 is known to be mainly distributed in proximal renal tubule and -1, 4-galactosyltransferase) knockout) showed no obvious physical and chemical abnormalities. Gb3 is known to be mainly distributed in proximal renal tubule and

Conclusions: These results indicate that targeted inhibition of PRC2 can improve renal function and promote the survival and proliferation of renal tubular cells through mechanisms associated with inhibition of p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α.

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PO0355
De Novo NAD+ Biosynthesis May Promote AKI Resistance
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Background: Acute kidney injury (AKI) is a wide-spread, costly condition with no treatment. Renal energy metabolism impairment is a key feature of AKI. Nicotinamide adenine dinucleotide (NAD+) plays a critical role in maintaining ATP and regulating energy metabolism. It is produced from three pathways: dietary tryptophan, niacin, and NAD+ recycling. Ischemic AKI suppresses de novo NAD+ biosynthesis from tryptophan, including the bottleneck enzyme,quinoline phosphoribosyl transferase (QPRT). QPRT +/- mice have worse AKI after ischemia-reperfusion (IRI). It is unknown if these disturbances are specific to ischemia, whether QPRT suppression contributes to AKI, or if restoration of this minor NAD+ pathway may be sufficient to improve AKI.

Methods: Nephron-specific conditional QPRT over-expressing mice were created (Pax8-rTαA, tetO-QPRT, iNephQPRT). Cisplatin was administered to induce AKI. Parallel AKI was induced in QPRT +/- and QPRT +/- mice. QPRT expression was measured via qPCR. AKI severity was assessed with serum biochemistries and histology.

Results: Toxic AKI suppressed QPRT mRNA proportionally to AKI severity (Fig C.D). QPRT +/- mice were more susceptible to toxic AKI (Fig A). Conversely, iNephQPRT mice exhibited protection against AKI (Fig B).

Conclusions: QPRT suppression is necessary for severe nephrotoxic injury, and renal tubular QPRT augmentation is sufficient to ameliorate injury. Given that de novo NAD+ synthesis is considered a minor contributor to steady-state NAD+ balance, these results provide striking evidence of this pathway’s importance to renal health during acute stress. Further, these findings implicate de novo NAD+ biosynthesis suppression as a pathogenic event in a mechanistically distinct context compared to IRI. Elucidating the regulation of QPRT and NAD+ homeostasis may be critical to understanding AKI physiology and developing novel therapies.

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Underline represents presenting author.
Results: Compared with WT C57 mice, A4GALT KO mice were more sensitive to AA administration. A4GALT KO mice began 6 days of administration, A4GALT KO mice began 5 days of administration, which showed significant weight loss. On day 9, more severe renal tubular injury pathological changes, significantly increased urine leukocytes and ketones were detected in A4GALT KO mice. The proliferation of bladder transitional epithelial cells was significantly increased in AA treated WT and A4GALT KO C57 mice, accompanied with fibrin deposition, vascular dilatation and a small amount of inflammatory cell infiltration in the bladder compared with that in the untreated group. There was no significant difference in bladder changes between WT and A4GALT KO groups after AA administration.

Conclusions: Our finding uncovered that Gb3 was protective in AA-mediated renal tubular necrosis and its presence reduces kidney injury. We will further explore its specific mechanism in the following study.

Funding: Other NIH Support - Burroughs Wellcome Fund

PO0357
The Effect of Ischemia-Reperfusion Injury on Nuclear-Reduced Glutathione Levels in Kidneys from Old Female Lewis Rats
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Background: The purpose of the study was to determine the effect of ischemia/reperfusion injury (IRI) on nuclear reduced glutathione (GSH) levels in kidneys from old rats. GSH is the major antioxidant inside cells, and a decrease in GSH levels would contribute to the damage caused by free radicals that are elevated in IRI. There is limited information on the effect of IRI on nuclear GSH levels.

Methods: Anesthetized old female Lewis rats (22 months of age) were used in the study. The left and right renal pedicles was clamped for 60 min, followed by 60 min of reperfusion. Experimental Group (n=5). The kidneys were then harvested, separated into cortex and medulla, and homogenized. Kidneys in the Control Group (n=5) were not subjected to IRI before being harvested. The nuclear fractions were isolated using differential centrifugation, and GSH levels were measured using a spectrophotometric assay. The water contents of the cortex and medulla were determined to allow GSH levels to be expressed as nmol/g kidney dry weight. A Student’s T-test was used to compare the groups, and statistical significance was determined at p<0.05. All data shown as X ± SEM.

Results: Nuclear GSH levels were significantly decreased in both the kidney cortex and medulla of the Experimental Group when compared to the Control Group. Nuclear GSH levels in the cortex decreased by 28%, with nuclear GSH being 535 ± 56 nmol/g kidney dry wt in the Control Group, and decreased to 385 ± 23 nmol/g kidney dry wt in the Experimental Group exposed to IRI. Nuclear GSH levels in the medulla decreased by 54%, with nuclear GSH being 676 ± 72 nmol/g kidney dry wt in the Control Group, and decreased to 399 ± 29 nmol/g kidney dry wt in the Experimental Group exposed to IRI.

Conclusions: After 60 min of ischemia, nuclear GSH levels in rat kidney cortex and medulla did not return to normal levels after 60 min of reperfusion. The results suggest that the nucleus is experiencing major oxidative stress and damage caused by free radicals in IRI, and this may be contributing to the renal dysfunction seen in IRI.

PO0358
Metabolomics Reveals the Efficacy of Limonin on Mitigating Cisplatin-Induced AKI
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Background: In the clinic, acute kidney injury (AKI) is one of the most severe cisplatin side effects, limiting its use in cancer therapy. Our previous study demonstrated that Limonin, a triterpene compound extracted from citrus, alleviated cisplatin-induced AKI. However, the involved mechanisms remain largely unknown. In this study, we elucidated how Limonin mitigates cisplatin-induced AKI from a new perspective, metabolomics.

Methods: A total of 30 mice were divided into three groups: Sham, Cisplatin + vehicle, and Cisplatin + Limonin. Limonin was administrated once daily via oral gavage started 3 days before cisplatin injection. At 72 h after cisplatin injection, kidney tissues started 3 days before cisplatin injection. At 72 h after cisplatin injection, kidney tissues were collected for metabolomics. Metabolomics was performed using Trace 1310 Gas Chromatograph coupled equipped with an AS 1310 autosampler connected to a TSQ 8000 triple quadruple mass spectrometer.

Results: After AKI, Limonin significantly preserved serum creatinine and blood urea nitrogen levels and ameliorated kidney tubular injury, compared with vehicles. Kidney samples were analyzed using UPLC/Q-TOF. A total of 302 metabolites were detected. The principal component analysis indicated that these metabolites could be well separated, reflecting the changes of metabolite distribution after treatment of Limonin. Multivariate statistical analysis further identified 34 endogenous differentially expressed metabolites within the days 5 of administration. Our findings suggested that phenylalanine, asparagine and tryptophan biosynthesis, phenylalanine metabolism, and linoleic acid metabolism were the top disturbed metabolic pathways amid the AKI repair process. These metabolic pathways are tightly correlated with oxidative stress, inflammatory response, and energy metabolism. Specifically, Limonin reduced Linoleic acid content, a major metabolite in the linoleic acid metabolism with oxidative stress, inflammatory response, and energy metabolism. Specifically, our findings revealed that GSH levels in the cortex decreased by 29 nmol/g kidney dry wt, with nuclear GSH being 56 nmol/g kidney dry wt in the Control Group, and increased to 79 nmol/g kidney dry wt in the Experimental Group exposed to IRI.

Conclusions: Our findings revealed how Limonin mitigates cisplatin-induced AKI from a new perspective, metabolomics.

Funding: Other NIH Support - Burroughs Wellcome Fund

PO0359
Role and Regulatory Mechanism of Adropin in AKI by Regulating PKD4
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Background: Oxidative stress and inflammation are the important biological mechanisms of the development of ischemic Acute kidney injury (AKI). Pyruvate Dehydrogenase Kinase 4 (PKD4) is a key enzyme in the process of glucose oxidation, which can inhibit glucose oxidation. Adropin, a secreted protein encoded by Energy Homeostasis Associated (ENHO) gene, is involved in the pathogenesis and pathological process of metabolic and inflammatory diseases and other diseases, can inhibit oxidative stress and inflammation, but its mechanism is unclear in AKI.

Methods: In vitro, HK2 cells were incubated with rotenone to mimic AKI. Western Blotting revealed that with that in the untreated group. There was no significant difference in bladder changes between WT and A4GALT KO groups after AA administration.

Conclusions: Our findings uncovered that Gb3 was protective in AA-mediated renal tubular necrosis and its presence reduces kidney injury. We will further explore its specific mechanism in the following study.

Funding: Other NIH Support - Burroughs Wellcome Fund

PO0360
Targeting Myeloid Ferritin Heavy Chain (FTH) in Rhabdomyolysis-Induced AKI
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Background: Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function and significantly impacts mortality. During rhabdomyolysis, muscle injury leads to release of myoglobin, causing an increased heme/iron delivery to the kidney, leading to AKI. Iron exacerbates oxidative stress and causes cell death. Kidneys respond to increased iron by inducing ferritin heavy chain (FTH) expression. FTH is a ferrooxidase
that converts ferrous iron into ferric form. Distinct myeloid populations promote injury and deletion of macrophages protect against rhabdomyolysis. Myeloid cells express high levels of F4/80 and mediate iron recycling. Therefore, we tested the hypothesis that myeloid F4/80 confers protection against rhabdomyolysis-induced AKI.

**Methods:** To induce rhabdomyolysis, female mice (10-12 weeks) deficient in myeloid F4/80 (FtH<sup>+/-</sup>) and floxed controls (FtH<sup>-/-</sup>) were deprived of water for 16 h and administered 50% glycerol via intramuscular injection into hindlimbs (7.5 or 11 ml/kg body weight). Mice were harvested at 1-, 3-, or 7-days post-glycerol. Kidney function and injury were evaluated by serum creatinine, and kidney injury marker 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) expression, respectively. Kidneys were analyzed for markers of cell injury/death (JNK, NF-kB, caspase 3, and TUNEL positivity and fibrosis).

**Results:** Rhabdomyolysis led to a significant loss in kidney function and an increase in kidney injury (NGAL and KIM-1) in all groups of mice. However, at 7 days, while these markers returned to baseline in FtH<sup>+-/-</sup> mice, there was a persistent tripling of these markers in FtHLysm<sup>-/-</sup> kidneys. Kidneys were analyzed for markers of cell injury/death (KIM-1, calcium-binding protein A8 (S100A8)), cleaved caspase 3 (CC3) and TUNEL positivity and fibrosis.

**Conclusions:** Our findings demonstrate that while myeloid FtH deletion does not impact acute injury following rhabdomyolysis, it mitigates injury progression and promotes recovery. Current studies are aimed at using single cell RNA sequencing approaches to identify key pathways that are activated during the resolution phase following rhabdomyolysis.

**Funding:** NIDDK Support

**PO0361**

**Nicotinamide Retains Klotho Expression and Ameliorates Rhabdomyolysis-Induced AKI**

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**Background:** Acute kidney injury is a severe complication of rhabdomyolysis. Inflammation plays a critical role in the pathogenesis of rhabdomyolysis-induced AKI. Nicotinamide, a form of vitamin B3 and a precursor of nicotinamide adenine dinucleotide, has been shown potent anti-inflammation effects. Klotho is a tubular highly expressed renoprotective protein. Therefore, we explored the effect of nicotinamide on rhabdomyolysis-induced AKI and the underlying mechanisms.

**Methods:** We used glycerol-induced rhabdomyolysis mouse model to observe the effect of nicotinamide on kidney injury. Western blot, chromatin immunoprecipitation and small interfering RNA were used to evaluate the role of Klotho in nicotinamide-related renoprotection.

**Results:** The results showed that nicotinamide attenuated kidney injury in rhabdomyolysis. Moreover, nicotinamide effectively blocked the recruitment of NF-kB, NCO and HDAC1 to the promoter of Klotho and preserved Klotho expression. More importantly, renoprotection effect of nicotinamide was abrogated when Klotho was knockdown by small interfering RNA.

**Conclusions:** Our study demonstrates that Klotho preservation is essential for the renoprotection effect of nicotinamide and provides a new preventive strategy for rhabdomyolysis-induced AKI.

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involve oxidative and endoplasmic reticulum (ER) stress, inflammation, and cell death. We have shown that a single cutaneous exposure to arsenicals causes acute kidney injury (AKI) in mice as evidenced by increased serum and urinary biomarkers of AKI. Intrarenal heme oxygenase-1 (HO-1), a protective anti-oxidant enzyme, is also upregulated as a response to injury in addition to ATF4 and CHOP, molecules involved in regulation of cell death and apoptosis.

Methods: To interrogate the precise role of HO-1 in arsenical-induced AKI, we exposed HO-1 knockout mice (HO-1<sup>−/−</sup>) and wild-type controls to renal artery occlusion (RAO) and reperfusion, and every 24 hours for 7 days. Serum creatine (sCre) and urine protein (sUr) were collected 24 hours and 7 days following ischemia to assess renal function. At day 7, kidney sections from treated rats (p<0.05) were stained with TUNEL, and measurement of peritubular capillary density by immunofluorescent staining.

Results: Our data show that HO-1 deficiency results in worse kidney damage post-RAO exposure, suggesting it is a targetable enzyme for intervention. Utilizing a novel small molecule inducer of HO-1 created in collaboration with Southern Research, we demonstrate that 1 hour pre-treatment with SR-37618 diminishes HO-1 induced ATF4 and CHOP expression in HEK-293 cells.

Conclusions: While further studies to assess the efficacy of SR-37618 in mouse models are ongoing, the data presented here provide evidence that HO-1 induction by SR-37618 is protective against arsenical-induced AKI. Moreover, small molecule inducers of HO-1 could potentially serve as a novel therapeutic for intervention in other forms of AKI.

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PO0364

Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Tubular Epithelial Cell Injury and Associated Renal Hemodynamic Responses

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Background: Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI). Drug toxic effects range from mild sub-lethal RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI. The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI. QST modeling is a promising method for translating cellular-level renal damage to clinical manifestations of AKI.

Methods: We developed a renalQSim, a QST model of drug-induced AKI that includes key cellular injury mechanisms and renal hemodynamic responses. At the cellular level, RenalQSim represents RPTEC life cycle, bioenergetics, and immune responses to renal toxicity. In vitro assays were used to parameterize key cellular injury mechanisms. At the systems level, RenalQSim model represents renal function and feedback mechanisms including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS). RenalQSim was employed to characterize the renal hemodynamic responses of drug-induced RPTEC in injuries in humans treated with cisplatin.

Results: At the cellular level, urinary biomarkers such as KIM-1 and ocGFR were used to represent cellular injury and death following cisplatin exposure. RenalQSim was able to capture the elevations in KIM-1 and ocGFR. The model also captured GFR decline and demonstrated that it occurs due to 1) increased Bowman’s pressure, 2) reduced filtration caused by decreased GFR due to RAAS activation and TGF mechanisms, and 3) lower renal perfusion pressure from excess sodium and water excretion. The model quantitatively relates cellular injury and biomarker changes with renal hemodynamic responses.

Conclusions: RenalQSim represents kidney function at cellular and organ levels in healthy and pathologic states caused by toxic drug effects. By describing drug-induced cellular injury and subsequent hemodynamic changes it can predict clinical responses during AKI.

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PO0365

Elastin-Like Polypeptide Vascular Endothelial Growth Factor (ELP-VEGF) Improves Renal Function and Decreases Inflammation Following Ischemia Reperfusion Injury in Mice

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Background: Acute Kidney Injury (AKI) represents a significant clinical concern and significant risk factor for the development of chronic kidney disease (CKD). AKI is associated with impaired renal function, increased inflammation and microvascular congestion. Specific fusion proteins between the elastin-like causes acute biopolymer and human VEGF-α (ELP-VEGF) efficiently target the renal vasculature and promotes vascular protection and angiogenesis, while potentially altering inflammatory processes. However, it is unknown if ELP-VEGF administration following ischemia-reperfusion mitigates injury, facilitates vascular protection and hastens recovery.

Methods: Male C57BL/6 mice were subjected to unilateral ischemia (IR) for 25 minutes. Post-ischemic animals were treated daily with either vehicle or ELP-VEGF (10μg/kg bw; i.p.) at reperfusion, and every 24 hours for 7 days. Serum creatine (sCre) and BUN were collected 24 hours and 7 days following ischemia to assess renal function. At day 7, kidney sections from treated rats (p<0.05) were stained with TUNEL, and measurement of peritubular capillary density by immunofluorescent staining.

Results: Increases in BUN following unilateral IR were significantly attenuated in the ELP-VEGF treated group compared with vehicle at both 24 hours (66% vs. 15%) and 7 days (4% vs. 19%) following ischemia (p<0.05). In ELP-VEGF treated mice, there was a significant reduction in Th17 cells (CD4+IL17+; 408236 vs. 182277 cells/g kidney: CD8+IL17+; 484483 vs. 99391 cells/g kidney), DC/Macrophages (12404078 vs. 4764147 cells/g kidney) and B Cells (16201355 vs. 7641714 cells/g kidney) compared with control.

Conclusions: ELP-VEGF represents a novel renoprotective therapeutic compound related to its anti-inflammatory and renovascular protective effects.

Funding: NIDDK Support

PO0366

Inhibition of PFKFB3 Alleviates Cisplatin-Induced AKI

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Background: Metabolism and its reprogramming may have influence on acute kidney injury (AKI) and subsequent kidney repair. 6-phosphofructo-2-kinase/fructose-2,6-biphosphate (PFKFB3) is an important rate-limiting enzyme in glycolysis. Recently, PFKFB3 has gained substantial interest as an attractive target for cancers and pulmonary hypertension therapy. However, the role of PFKFB3 in AKI remains poorly understood.

Methods: To investigate the role of PFKFB3 in cisplatin nephotoxic AKI, we established stable PFKFB3 knockdown rat renal tubular cell lines (RPTEC) and generated the kidney proximal tubule-specific PFKFB3 knock-out mice by crossing PFKFB3-floxed mice with PEPCK-CRE mice. PFKFB3-knockdown and wild-type RPTEC cells were treated with 20μM cisplatin for 24h in vitro, while PFKFB3-knock-out or wild type mice with 5-10 weeks were intraperitoneally injected with 30 mg/kg of cisplatin or vehicle.

Results: PFKFB3 was up-regulated in cisplatin-induced AKI models both in vitro and in vivo. In the mouse model, deficiency of PFKFB3 reduced cisplatin-induced kidney injury and improved renal functions. Moreover, genetic and pharmacological inhibition of PFKFB3 in RPTEC cells suppressed cisplatin-induced apoptosis. In addition, phosphorylated Erk1/2, phosphorylated p38 and phosphorylated NF-κB were decreased in PFKFB3 knockdown RPTEC cells compared to the vector group.

Conclusions: These results indicate that PFKFB3 is a key mediator of renal tubular injury in cisplatin-induced AKI and may be an effective therapeutic target for alleviating cisplatin nephotoxicity in chemotherapy.

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PO0367

Cilastatin Inhibits Renal Myoglobin Endocytosis and AKI Following Rhabdomyolysis

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Background: Muscle-derived myoglobin, a renal toxin, causes rhabdomyolysis-induced acute kidney injury (AKI) via megalin-mediated endocytosis into proximal tubule cells (PTs). Endocytosis kinetics and inhibition are poorly understood. We characterized myoglobin uptake in vivo, hypothesizing cilastatin, a putative megalin inhibitor, would prevent endocytosis akin to megalin knockouts.

Methods: Procedures in wild-type (WT) male C57BL/6 mice and inducible, PT-specific megalin-deleted mice (iMegKO) were approved by OHSU or PV AMC IACUC. FITC-myoglobin (FMb) and cilastatin (200 mg/kg) were injected retroorbitaly. Experimental rhabdomyolysis (ER) was induced via intramuscular injection of 50% glycerol (8 mL/kg). Glomerular filtration rate (GFR) was measured 24h later, and immunofluorescence and single-cell RNASeq were performed on renal tissue.

Results: FMb was observed in PTs 15 min post-injection in control mice; in iMegKO mice, FMb puncta were nearly absent (p<0.001). FMb puncta were reduced in cilastatin-treated WT mice without ER vs vehicle controls (p<0.0012). Cilastatin prevented AKI following ER, with 24h GFR 5x control (p<0.001). Cilastatin (50 μg/kg) increased GFR in iMegKO (p<0.09), but had a significant effect on ER-induced AKI in wild-type mice: GFR was 8x vehicle (p<0.03) while PT uptake of endogenous myoglobin decreased (p<0.05). A composite score of endocytosis related genes (endocore) showed significant antagonism (p<0.01). 

Conclusions: Cilastatin interference prevents ER-induced AKI by reducing myoglobin endocytosis; cilastatin recapitulates the effect in a megalin-inhibitory fashion. Alteration of endocytosis-related genes confirms this process is critical in rhabdomyolysis, and may suggest additional therapeutic targets. Future studies will also include cilastatin delivery timing, dosage, and formulation.

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159
PKM2-Specific Deletion in Myeloid Cells Ameliorates Renal Impairment by Alleviating Metabolic Changes in CaOx-Induced AKI

PO0368

Background: Metabolic reprogramming occurs in AKI, altering the ability of myeloid cells to adapt to the pro-inflammatory environment. PKM2, a key regulator of glycolysis, plays a role in this reprogramming. We investigated whether deletion of PKM2 in myeloid cells would interfere with renal metabolism and exert protection in calcium oxalate (CaOx) crystal-induced acute kidney disease (AKI).

Methods: Myeloid-specific PKM2-knockout mice (PKM2fl/fl) and their Cre-negative littermates (PKM2+/-) and their Cre-negative littermates (PKM2+) were examined in AKI. PKM2 in bone marrow-derived macrophages was assessed by FACS. Serum creatinine, blood urea nitrogen in mice exposed to cisplatin.

Results:
1. PKM2 expression in bone marrow-derived macrophages was reduced in PKM2fl/fl mice compared to PKM2+/- and PKM2+ mice.
2. The number of F4/80+CD11b+ cells in kidneys were similarly elevated by CaOx in both PKM2fl/fl and PKM2+/- mice.
3. In PKM2fl/fl mice, intrarenal CaOx deposition impaired renal function, as well as increased the expression of IL-6, NGAL, KIM-1, HK2, CPT1a and CPT2 mRNA expression (quantitative PCR), macrophage number/area, and kidney function prospectively.

Conclusions: PKM2 deletion in myeloid cells ameliorated renal impairment by alleviating metabolic changes in CaOx-Induced AKI.

Ginsenoside Rg3 Attenuates Ischemia Reperfusion-Induced Renal Injury in Mice via Induction of Autophagy Flux

PO0370

Background: Ginsenoside Rg3 (Rg3) has been shown to provide protective effects via various mechanisms. However, whether the renoprotective effect and the role of autophagy are not clearly evaluated. This study investigated Rg3 induces autophagy flux and reduces renal cell death in renal ischemia reperfusion injury (IRI).

Methods: C57Bl/6 mice were divided into the following groups: sham; Rg3 treated sham; saline treated IRI mice; Rg3 treated IRI mice. Kidneys and blood were collected 24h after operation of mice (sham and IRI operation). Renal function, kidney histology, and the protein expression of autophagy signals were evaluated.

Results:
1. In IRI mice, the levels of BUN and s-Cr were increased, compared to sham. The Rg3 treatment decreased the BUN and s-Cr in IRI mice.
2. BUN and s-Cr treatment decreased the renal injury score including the renal tubular cell detachment and necrosis in IRI mice.
3. Rg3 treated IRI mice showed significantly less oxidative stress and apoptosis as compared to IRI mice.

Conclusions: Rg3 has renoprotection against renal IRI injury via enhancement of autophagy flux.

A Novel Immunomodulatory Peptide Suppresses Inflammatory Macrophages and Mitigates AKI

PO0371

Background: Monocytes/macrophages are known to play a critical role in the pathogenesis of acute kidney injury (AKI), as large numbers of monocytes are recruited to the kidney and differentiate into pro-inflammatory macrophages (M1 phenotype) after injury. Although targeting macrophages has emerged as a promising therapeutic strategy for AKI, the effective treatment is still limited. We previously identified a novel peptide, the MPS peptide, which targets the signaling molecule myristoylated alanine-rich C-kinase substrate (MARKS), a central inducer of M1 macrophages. In this study, we have employed this novel peptide to determine if MARCKS inhibition reduces kidney injury.

Methods: High-dimensional single-cell mass spectrometry was used to reveal immune profiling in an AKI mouse model. Both commercial macrophage cell lines and primary macrophages isolated from peripheral blood mononuclear cells were utilized in this study for gene expression analysis. In vitro and in vivo inflammatory activities of the MPS peptide were confirmed by Western blots, real-time reverse transcription-polymerase chain reaction (RT-qPCR), flow cytometry, ELISA cytokine assays, and immunohistochemistry.

Results:
1. Analysis of the single-cell RNA sequencing data has identified that the immune microenvironment of injured kidneys is associated with the expansion of monocytes/macrophages, particularly M1 macrophages. We next show that an elevated abundance of phospho-MARKS in macrophages upon cisplatin treatment and this increase occurred in parallel with an increase of M1 markers as well as upregulation of inflammatory cytokines and markers of necroptosis in cisplatin-exposed kidneys. Mechanistically, we demonstrate that MPS peptide had an inhibitory effect on cisplatin-induced phosphorylated MARKS, p65 phosphorylation, and NF-kB activation in macrophages.

Conclusions: Our results suggest that MARCKS phosphorylation is a novel NF-kB activator in pro-inflammatory macrophages and also presents a proof of concept for the use of MPS peptide as a renal protection agent for AKI.
Results: Urinary glucose excretion was comparable in both treatment groups indicating comparable SGLT-2 inhibition. Comparing GFR surrogate markers after IRI (sCr and BUN). At all investigated time points after IRI, sCr and BUN were higher in the IRI+canaagli Zion group than placebo-treated rats, whereas the empagliflozin group did not differ from the placebo group. IRI led to tubular dilatation and necrosis. Empagliflozin was able to reduce that finding whereas canagliflozin had no effect. Renal expression of KIM-1 increased after IRI and empagliflozin but not canagliflozin normalized KIM-1 expression (Figure). IRI reduced urinary microRNA-26a excretion. Empagliflozin but not canagliflozin was able to restore normal levels of urinary miR-26a.

Conclusions: In conclusion, our study confirmed the observations made in the CREEDENCE and the EMPA-REG OUTCOME trials. The empagliflozin effects on KIM-1 and miR-26a might indicate beneficial regulation of inflammation and innate immune response. Our data should stimulate clinical studies analyzing whether empagliflozin is a preferable SGLT-2 inhibitor in patients at high AKI risk.

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organoids compared to control group (n=3;p<0.05). LDH assay also revealed that the additional addition of acetaminophen attenuated the impact of CFH on organoids by decreasing the toxicity by ~23% within the organoids (p value<0.0001).

**Conclusions:** Human kidney organoids can be used to model sepsis-induced AKI. CFH treatment induced toxicity and reduced viability of the human kidney organoids. Both ascorbate and acetaminophen had protective effects on CFH-induced organoid injury.

**Funding:** Private Foundation Support

**PO0376**

**Pulsed Ultrasound Reduces Oxidative Stress-Induced Disruption of Epithelial Barrier in Sepsis-AKI**

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**Background:** Oxidative stress disrupts epithelial junctions leading to increased paracellular permeability and kidney dysfunction. We previously showed that pulsed ultrasound (pUS) reduced inflammation and kidney injury. We hypothesized that pUS mitigates renal injury by maintaining epithelial tight junctions. Here, we utilized lipopolysaccharide (LPS) induced sepsis to create acute kidney injury (S-AKI) in a mouse model and RAW 264.7 cells to investigate the effects of pUS on the epithelial tight junction barrier and renal macrophages.

**Methods:** C57BL/6 mice received pUS 24 hrs before LPS treatment. The parameters of pUS therapy followed the protocol previously published by us (PMID: 23907510). Following pUS treatment, mice received a single injection of LPS (5 mg/kg, ip). Animals were euthanized at increasing time intervals for measurement of mRNA expression and kidney histopathology. Kidney histopathological changes were observed by using PAS staining. Co-staining with TUNEL and cleaved caspase-3 was used to assess kidney injury. For in-vitro assays, RAW cells were seeded onto 4-well plates and incubated for 24 hrs at a density of 5 × 10^5 per well. Cells were treated with LPS (100 ng/ml) in serum-free DMEM for 2 hrs.

**Results:** LPS induced kidney injury and apoptosis, as observed by PAS and TUNEL staining, was attenuated by pUS. Co-staining with PDSD95 (post-synaptic scaffolding density protein 95) and ZO-1 (zona occludens-1) showed both were expressed in kidneys. LPS also induced significant loss of PDSD95 accompanied by a reduced mRNA expression of nuclear factor erythroid 2-related factor 2 (NRF2) and activated macrophages. The structural changes, extent of loss of PDSD95 and NRF2, as well as macrophage infiltrate were all partially reversed by prior pUS treatment. In cultured RAW cells, pUS upregulated the expression of NRF2 and heme oxygenase-1 (HO-1), and attenuated CD68-positive macrophage signals.

**Conclusions:** pUS protected kidneys from LPS-induced S-AKI by preserving antioxidant NRF2 expression and attenuating oxidative stress-induced disruption of epithelial tight junctions.

**Funding:** NIDDK Support

**PO0377**

**Hypertensive Diabetic Kidney Disease Increases the Severity of Experimental AKI**

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**Background:** Patients with diabetic kidney disease (DKD) are at increased risk of severe AKI and adverse outcomes. Since DKD may alter cellular and therapeutic responses in AKI, there is a need to establish a model to evaluate the mechanisms and therapeutics of AKI in the context of DKD. These studies address this deficiency by characterizing AKI in transgenic mice with renin-induced hypertension and progressive DKD.

**Methods:** Hypertensive male transgenic TThRen (TR+) mice, which over-express renin in the liver, were treated +/- streptozotocin to induce diabetes (DM). Tail cuff BP; urinary albumin/creatinine ratio (ACR); BUN; and transdermal GFR (tGFR) were followed by serial BP, BUN, ACR and tGFR measurements over 8 wks.

**Results:** After ischemia-reperfusion AKI (IR-AKI), mice underwent bilateral IR-AKI at 32 wks, followed by serial BP, BUN, ACR and tGFR measurements over 8 wks.

**Results:** ND and DM TR+ mice had increased albuminuria (31wk ACR, mg/mg: ND TR+ vs. +, 17.7 (2.0) vs. 498.2 (325.2), p<0.0001; DM TR+ vs. +, 136.7 (30.3) vs. 1028 (420.3) p=0.01), with no significant difference between DM and ND TR+ mice. BP was elevated in TR+ mice, with no difference between DM and ND mice, but there was a decrease in GFR in DM TR+ vs. ND TR+ over time (2 way ANOVA, p=0.05). After IR-AKI, DM TR+ mice had more severe injury than DM TR- mice (e.g.: day1 BUN, ng/dl: DM TR+ vs. -, 56.7 (8.6) vs. 95.1 (11.8), p<0.01), but there was no difference in severity of injury in ND TR+ and - mice. This was associated with a progressive increase in albuminuria, but after 14 days, no difference in GFR in DM TR+ vs. - mice, and no change in albuminuria or GFR in ND TR+ vs. - mice up to 8 weeks after IR-AKI.

**Conclusions:** Hypertensive DM and ND mice develop albuminuria, but only hypertensive DM mice develop reduced GFR consistent with progressive DKD. After optimizing renal pedicle clamp times to induce similar injury, only hypertensive DM mice had increased injury and progressive nephropathy after IR-AKI, as determined by increased albuminuria, compared with non-hypertensive DM and both hypertensive and non-hypertensive ND controls. This may mimic human disease as there is increased injury and progressive DKD after IR-AKI mice with pre-existing DKD.

**Funding:** Other U.S. Government Support

**PO0378**

**Kidney-Specific Intestinal Alkaline Phosphatase (IAP) in Transgenic Mice Protects Lipopolysaccharide (LPS)-Induced Inflammation and Renal Failure**

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**Background:** LPS is a major player in septic AKI. However, LPS can be dephosphorylated to an inactive form by IAP. We generated kidney specific IAP transgenic mice (Tg) to test whether the targeted increase in IAP can decrease inflammation and improve renal function.

**Methods:** Tg mice were developed in C57Bl6 background using human chimeric IAP under the control of villin promoter making them kidney specific albeit some expression was also observed in the intestine. The 3' prime end of the transgenic codon had a cDNA fragment to distinguish human IAP from resident mouse IAP. Tg and non-transgenic littermates (Wild type, WT) were given 10 mg/kg LPS. Wild type control (Con) received saline. Renal function tests, plasma BUN creatinine, proteinuria, and albuminuria were performed. Plasma, Kidney, and liver were harvested after 12 hours for western blots and ELISA. Electron microscopy (EM) was done to evaluate podocytes.

**Results:** Serum creatinine and BUN were 2.5 and 3 fold higher in WT compared to Con (p<0.01), the increases were attenuated in Tg (p<0.05). In WT proteinuria and albuminuria were 3 and 5 fold higher than Con (p<0.05) these were attenuated in Tg (p<0.05). Cytokines (IL-1β, IL-6, and TNFα) in the liver, kidney, and plasma of WT after LPS injection was 2 to 4 fold higher than Con. However, in the liver of Tg+LPS, only TNFα was significantly reduced. Plasma and kidney cytokines of Tg+LPS were significantly lower than WT+LPS (Fig). The reduction of cytokines in the kidney of Tg+LPS was more profound than the plasma of Tg+LPS. Podocyte effacement in Tg mice was less severe than WT. We could detect cmyc in plasma and kidney in Tg mice.

**Conclusions:** This study shows targeted increase of IAP in the kidney can abate LPS mediated deterioration of renal function, inflammation, and podocyte effacement. IAP has been shown to be released after LPS administration perhaps as a protective mechanism. An increase in plasma cmyc after LPS injection indicate that human IAP could have been secreted in the blood from the kidney or intestine. This may have decreased the inflammatory burden in the plasma.

**PO0379**

**Pretreatment with Low-Dose Lipopolysaccharide Attenuates Ischemia Reperfusion-Induced Vascular Congestion Through Vasocostriction of the Outer Medulla During Reperfusion**

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**Background:** Vascular congestion in the renal outer medulla (OM) is common in acute organs injured after LPS administration and has been shown to be a protective mechanism. An increase in plasma cmyc after LPS injection indicate that human IAP could have been secreted in the blood from the kidney or intestine. This may have decreased the inflammatory burden in the plasma.

**Methods:** To test this hypothesis, male WKY rats (12wks) were pretreated (i.p) with 1mg/kg LPS (n=6) or saline control (n=7) daily for 3 days. Rats were then anesthetized, and Transonic Laser Doppler probes were inserted in the cortex and OM. Regional kidney blood flow was then measured over 10 minutes of baseline, 45 minutes of renal artery clamping and 30 minutes of reperfusion.

**Results:** There were no differences in baseline blood flow between rats pretreated with low dose LPS or saline control (p=0.7). The return of blood flow to the cortex was gradual (p<0.0001), reaching a plateau following 10 minutes of reperfusion in both groups (p<0.98). The return of blood flow to the OM, however, rapidly returned to baseline levels within 1 minute of reperfusion only in control animals (1 min: 0 to 0.43AU). In contrast, OM blood flow returned slowly in LPS treated rats (1 min: 0 to -0.08AU) and did not return to baseline levels during the 30-minute reperfusion period (pinteraction = 0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Our data indicate that LPS pre-treatment, paradoxically, slows the early phase of the AKI progression through regulation of cytokines. This effect attenuates medullary congestion by allowing RBCs in the shared venous circulation to clear. These findings support the hypothesis that backfilling of the renal medullary circulation before cortical reperfusion is restored, is responsible for the development of vascular congestion. Our next studies will focus on renal myomechanics after ischemia may prevent much of the injury associated with acute kidney injury.

Funding: NIDDK Support

PO0380

Dexamethasone Attenuates Kidney Ischemia Reperfusion Injury in SD Rats by Mediating M1 Macrophage Cytochrome Production

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Background: Published evidence suggests a beneficial effect of adjunctive corticosteroid therapy on time of withdrawal from ventilation and time in ICU, and as a faster reversal of septic shock. Studies in rodent models of acute kidney injury (AKI) have demonstrated a protective role of dexamethasone (Dexa), however its mechanism in attenuation of AKI is not clearly understood. Because M1 macrophages play role in the early stage of sepsis and ischemic kidney injury by producing proinflammatory cytokines contributing to AKI progression, we investigated the effect of Dexa during AKI on M1 polarized macrophages and kidney tubular epithelial cells.

Methods: Bilateral kidney Ischemia Reperfusion (IR) (30 minutes) was performed in 20 male SD rats (n=10/group). Dexamethasone (0.2 mg/kg) was injected IP 30 min before IR. Plasma cytokines TNFα, IL-1β, IL-6, and IL-10 were measured at 4 and 24 hours after IR. The monocyte monocytic cells TNF was differentiated for 72h after a 4h pulse of 20 ng/mL TNF. The media was then collected from the supernatant of HK-2 cells and used as media for tubular epithelial cells. Pretreatment of rats with Dexa reduced plasma creatinine (2 vs 1 mg/dL), urea nitrogen (18 vs 13 mg/dL), and creatinine clearance (70 vs 80 mL/min). In addition, in the absence of Dexa, Macrophage-conditioned keratinocyte media was then collected from the supernatant of HK-2 cells (a human kidney tubular epithelial cell line) in a hypoxic chamber (0.2% O2) for 48 hrs. Apoptosis of HK-2 cells was evaluated by determining Caspase 3/7 activity.

Results: Pretreatment of rats with Dexa reduced plasma creatinine (2 vs 1 mg/dL), BUN (121 vs 96 mg/dL) and decreased iGFR (0.5 vs 0.8 mL/min) at 24 hours post IR. Plasma cytokines known to be produced by M1 macrophages such as IL-1β and IL-6 were significantly reduced at 4h while MCP-1 was reduced 4 and 24h after IR. HK-2 cells treated with conditioned media obtained from M1 macrophages in the presence of Dexa and hypoxic conditions showed reduced caspase 3/7 activity.

Conclusions: Our data demonstrate that Dexa has a reparative effect in SD rat with IR-induced AKI. The observed beneficial effect of Dexa seems to involve an indirect anti-apoptotic effect on tubular epithelial cells and potentially a reduction of cytokine production by M1 macrophages.

PO0381

IL-33/ST2 Alarmin Signaling Axis in Myeloid Cells Regulates Kidney Injury

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Background: Macrophages are a heterogeneous class of cells that play a vital role in inflammation, repair and fibrosis post-injury; however, their role in early and late phases of injury is not well understood. IL-33 is a nuclear-localized alarmin cytokine that is released upon tissue damage and targets IL-1 receptor-like 1 (IL1RL1) or ST2. Myeloid cell-specific deletion of ST2 decreased expression of inflammasome markers, decreased absorption of FITC-dextran and decreased expression of tight junction proteins ZO 1 and claudin in the jejunum and ileum of CCl4 and CCl4+L cohorts suggesting increased intestinal barrier permeability. Curcumin treated, CCl4+L+CU group had decreased expression of inflammasome markers, decreased intestinal permeability and tissue injury are not fully elucidated. We aimed to explore the potential crucial genes and pathways involved in the pathogenesis of IRI/AKI by the bioinformatics method.

Methods: We extracted two gene expression profiles (GSE87024 and GSE34351) from the GEO database of wild-type mice and the early onset of the IRI-AKI. Differentially expressed genes (DEGs) were identified from the two expression profiles, enriched with gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs. Then we applied Gene set enrichment analysis (GSEA) methods to detect the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plug-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA-TF, drug-gene interaction networks to find the potential therapeutic targets.

Results: We extracted a total of 239 and 384 DEGs in GSE87024 and GSE34351 respectively, with the 73 same DEGs. GO and KEGG enrichment analysis of the DEGS further detected the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plug-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA-TF, drug-gene interaction networks to find the potential therapeutic targets.

Conclusions: Although curcumin has a significant anti-inflammatory property its systemic anti-inflammatory effect is limited by its poor bioavailability. We postulated that pre-treating mice with curcumin mitigates renal inflammation and reduces inflammatory burden in the circulation which helps in preserving liver and kidney function.

PO0383

Identification of Hub Genes and Pathways of Ischemia-Reperfusion Injury and AKI by a Bioinformatics Method

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Background: Ischemia/reperfusion injury (IRI) is the most common cause of acute kidney injury (AKI). However, mechanisms underlying the rapid loss in kidney function and tissue injury are not fully elucidated. We aimed to explore the potential crucial genes and pathways involved in the pathogenesis of IRI/AKI by the bioinformatics method.

Methods: We extracted two gene expression profiles (GSE87024 and GSE34351) from the GEO database of wild-type mice and the early onset of the IRI-AKI. Differentially expressed genes (DEGs) were identified from the two expression profiles, enriched with gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs. Then we applied Gene set enrichment analysis (GSEA) methods to detect the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plug-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA-TF, drug-gene interaction networks to find the potential therapeutic targets.

Results: We extracted a total of 239 and 384 DEGs in GSE87024 and GSE34351 respectively, with the 73 same DEGs. GO and KEGG enrichment analysis of the DEGS further detected the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plug-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA-TF, drug-gene interaction networks to find the potential therapeutic targets.

Conclusions: Our study focused on the early IRI-AKI by firstly adopted RRA analysis to combine DEGs in different datasets, identified hub genes and pathways. We further detected the potential therapeutic targets of the IRI-AKI such as curcumin and staurosporine.
PO0384

Resident Macrophages Limit IL-6 generation to Protect Against Septic AKI

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Background: The most common cause of acute kidney injury (AKI) in critically ill patients is sepsis. There are currently no treatments for septic AKI. Intra-renal macrophages include both tissue-resident (CD11b(lo) F4/80(lo)) and infiltrating (CD11b(hi) F4/80(hi)) populations. The role of resident and infiltrative macrophages in septic AKI pathogenesis remains unclear. As resident macrophages are reported to contribute to tissue repair following injury, we hypothesized that selective depletion of resident macrophages would worsen septic AKI.

Methods: Resident macrophages were selectively depleted via diphtheria toxin injection in CD11cCre(lo)/C3XCR1(hi) (RM KO) mice compared to CD11cCre(lo)/C3XCR1(lo) (RM WT) mice. RM WT and RM KO mice were subjected to sham or cecal ligation and puncture (CLP) sepsis. Kidney injury was assessed by serum creatinine and histologic injury scoring. Cytokine mRNA and protein levels in the serum and kidney were measured by RT-PCR and ELISA. Fluorescent cell-sorting and single cell RNA sequencing were sequenced to profile gene expression following CLP in various intra-renal cell lineages.

Results: After CLP, resident macrophages expressed high levels of anti-inflammatory genes including interleukin 1 receptor antagonist (IL1rn), known to suppress IL6 production. Therapy ameliorated septic AKI in RM KO mice (Fig. 1). RM KO mice elaborated higher circulating and kidney IL-6 levels. In turn, anti-IL6 therapy ameliorated septic AKI in RM WT mice. RM WT and RM KO mice were subjected to sham or cecal ligation and puncture (CLP) sepsis. Kidney injury was assessed by serum creatinine and histologic injury scoring. Cytokine mRNA and protein levels in the serum and kidney were measured by RT-PCR and ELISA. Fluorescent cell-sorting and single cell RNA sequencing were sequenced to profile gene expression following CLP in various intra-renal cell lineages.

Conclusions: This study revealed that kidney-specific deletion of Cullin 3 (Cul3) causes proximal tubule injury and fibrosis, but the mechanism is still unclear. Cul3 is essential for the ubiquitination and thus degradation of many critical proteins in several organs. This study aims to generate a Cul3-deficient human proximal tubule cell line using the CRISPR-Cas9 system. This model will allow us to understand the mechanistic role of Cul3 in the human proximal tubule.

Methods: CD107↑ proximal tubule cells were isolated by cell sorting from healthy human kidney cortex of a nephrectomy specimen. The primary proximal tubule cells were cultured and then immortalized using SV40LT and HTERT. Using different CRISPR-Cas9 approaches, Cul3 knockout clones were aimed to achieve. The most successful approach is depicted in the results section.

Results: The Cul3-specific guide RNA was cloned into pL-CRISPR.EFS.gfp containing restriction digests. Lentiviral particles were produced by transient co-transfection of HEK293T cells with lentiviral transfer plasmid, packaging plasmid psPAX2 and VSVG packaging plasmid pMD2. G. Using Transit-LT. Viral supernatants were collected 48–72 h after transfection, clarified by centrifugation, supplemented with 10% FCS and polybrene and sterile filtered. Cell transduction was performed by incubating the CD107↑ cells with viral supernatants. eGFP-expressing cells were single-cell sorted into 96-well plates. Expanded colonies were assessed for mutations with mismatch detection assay: gDNA spanning the CRISPR target site was PCR amplified and analyzed by T7EI digest. To determine specific mutation events on both alleles within the CRISPR-Lenti system, the PCR product was subcloned into the pCR4-TOPO vector. Minimal 6 colonies per CRISPR-clone were grown and sent for sanger sequencing. Results from qPCR and western blot confirmed Cul3 knockout. The clones were sent out for bulk RNA sequencing to reveal differentially regulated genes upon Cul3 deletion.

Conclusions: Cul3 is a major upstream player in different cell signaling pathways. This study will show the role of Cul3 in the proximal tubule of human kidney.

Funding: Government Support - Non-U.S.

PO0385

Untargeted Lipidomics Reveals the Potential Mechanism of Ferroptosis in HK-2 Cells Treated with Iohexol

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Background: The purpose of this study was to explore significantly different lipid markers that may be involved in the potential mechanism of ferroptosis in CIN.

Methods: Lipids were extracted from HK-2 cells (HK2-NC group), HK-2 cells treated with iohexol and Ferroportin-1 (a potent and selective inhibitor of ferroptosis, Fer-1)(HK2-I6+FeI group) according to MTBE method. An Untargeted Relative quantitative lipidomics method was performed, combined with the lipids Search software (Thermo Scientific). The lipidomics data analysis was performed using the LipidViewer software (Thermo Scientific). The difference in lipid species between HK2-I6 and HK2-NC groups, HK2-I6+FeI and HK2-I6 groups. The heat map result was generated using the Lipidomics Workflow Analysis (LWA) software (Thermo Scientific). The principal component analysis (PCA) and orthogonal partial least squares analysis (OPLS-DA) models were performed to explore the difference among the varied lipid species (HK2-I6+FeI group vs. HK2-NC group, 35 out of 42 PE, 38 out of 39 TG, 38 out of 39 SM, and all the 6 LPC increased with statistical significance, while 38 out 39 TG, 35 out of 42 PC, 35 out of 42 PG decreased significantly).

Results: Among the varied lipid species (HK2-I6+FeI group vs. HK2-NC group, 35 out of 42 PE, 38 out of 39 TG, 38 out of 39 SM, and all the 6 LPC increased with statistical significance, while 38 out 39 TG, 35 out of 42 PC, 35 out of 42 PG decreased significantly.

Conclusions: This study revealed that increased PC, decreased PE and TG may be involved in the potential mechanism of ferroptosis in the HK-2 cells treated with iohexol.

Funding: NIDDK Support, Other NIH Support - R08 GM132689 to JRP; Veterans Affairs Support

PO0387

Role of Megalin and Sex in AKI-CKD Transition due to Cardiorenal Syndrome Type 1

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Background: Cardiorenal syndrome type 1 (CRS-1) is acute kidney injury (AKI) due to rapid worsening of cardiac function. The megalin-mediated endocytic system is an important component of renal function which may influence AKI and which likely influences development of chronic kidney injury (CKD). As part of investigating AKI-CKD transition after CRS-1, we tested whether megalin deletion affects the severity of CRS-1 and consequential CKD.

Methods: Male and female proximal tubule-specific inducible megalin deletion mice (iMegKO, LR2P IIβ NDRG1.CreERT2) received tamoxifen (150 mg/kg) for 5 days, 16 days before cardiac arrest and cardiopulmonary resuscitation (CA/CPR). 24 hours after resuscitation, kidney proximal tubule cells were isolated by cell sorting from healthy adult male and female mice. Measuring proximal tubule cells were characterized. Immunofluorescence and immunoblotting were performed to quantify acute and chronic renal injury, fibrosis, and megalin expression.

Results: Tamoxifen only induced deletion of megalin in cre+ mice. Urine protein and urine albumin were increased by proximal tubule-specific megalin deletion, primarily low-molecular weight proteins. Specific megaclin ligands including RBP-4 were elevated in the urine. At baseline, GFR of iMegKO mice was higher than control mice (p<0.001 by student’s t-test, n=11-12/group). CA/CPR variables, including time to resuscitation and cardiac output were not different between groups (p=0.05 by one-way Anova, n=9-13/group). Body weight-corrected urine volume at 24 hours after CA/CPR or 49 days after CA/CPR were not different between iMegKO mice and cre- littermate control mice, both in male and female groups (p=0.05 by one-way Anova; for 24 hours, n=5/9/group, for 49day analysis, n=2/3/group). GFR at 24 hours and 49 days after CA/CPR was not different between iMegKO mice compared with littermate control mice (p=0.05 by one-way Anova; for 24 hours, n=5/6/group, for 49day analysis, n=2/3/group). In female, iMegKO didn’t mediate GFR at 24 hours or 49 days after CA/CPR (p=0.05 by one-way Anova; for 24 hours, n=2-3/group, for 49day analysis, n=3/group).

Conclusions: This study revealed that increased PC, decreased PE and TG may be involved in the potential mechanism of ferroptosis in the HK-2 cells treated with iohexol.
PO0388

Spatially Resolved Transcriptomics Reveal Temporal Dynamics of Gene Expression Changes in a Model of Female AKI

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Background: Preclinical studies of acute kidney injury (AKI) have focused on male rodents leaving a substantial gap in our understanding of AKI in females. Single cell transcriptomic studies are remarkably powerful, but the loss of positional information with tissue dissociation handicaps our interpretation. Therefore, we applied the 10X Genomics spatial transcriptomic solution, Visium, to investigate interactions between cell types in their physiological orientation during injury.

Methods: We performed bilateral ischemia reperfusion injury (Bi-IRI) on female C57BL/6J mice. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-labeled dextran.

Results: New analytic pipelines SPOTlight and Giotto, enriched with gene expression data from our previously published single cell RNA transcriptomic atlas of mouse injury, significantly enhanced the visualization and resolution of spatial data in our female Bi-IRI model. Spatial libraries detected 16,856 unique genes across all injury timepoints. Integration with scRNAseq increased resolution of specific underrepresented cell types, such as macrophages, T cells, and fibroblasts. Key visualization tools demonstrated changes in the temporal and spatial expression of differentiation markers, including Krt20 and Vim, after injury. Spatial interaction analyses of macrophages and T cell related genes, such as Lyn and Tmem30b, revealed dynamic cell type interaction changes in addition to specific interactions with a pro-inflammatory and pro-fibrotic proximal tubule injury induced cell state. We prioritized cell-cell interactions based on physical proximity and validated these results by immunofluorescence. We curated an online data visualization tool to provide broad access of this dataset to the community.

Conclusions: We present the first comprehensive spatial transcriptomic atlas for a female mouse model of AKI along a time course after ischemic injury. We leveraged this spatial transcriptomic dataset to investigate cell type interaction changes, revealing previously unknown cellular dynamics of macrophages and T cells in the proximal tubule.

Funding: NIDDK Support

PO0389

Single-Cell Sequencing of Immune Cells in AKI and Renal Fibrosis

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Background: Immune responses help determine outcome following acute kidney injury (AKI) and Chronic Kidney Disease (CKD) progression. Single Cell RNA Sequencing (scRNAseq) provides an unparalleled opportunity to uncover heterogeneity and provide new mechanistic understanding in AKI-CKD. We have performed scRNAseq of immune cells at specific timepoints mimicking human disease pathology in models of AKI and renal fibrosis.

Methods: Kidneys were harvested from three mice at each time point (Figure 1) mimicking disease states in AKI-CKD. Using a cell sorting strategy, CD45+ cells were isolated from whole kidneys and libraries were prepared on the 10X Genomics platform. scRNAseq was performed using the Illumina NextSeq 550 System. We conducted Genome mapping using Cellranger and zUMIs and downstream expression analysis was carried out using R and Seurat.

Results: 21,734 CD45+ve Cells were sequenced in total. Analysis of gene expression profiles delineated transcriptomic profiles in distinct sub-clusters of immune cells across disease states. Comparison of these demonstrated dynamic changes in immune cell compositions, recruitment and patterns of gene expression, in line with an immune response to AKI recovery and fibrosis. Heterogenous clusters of macrophages were seen in disease states, revealing an inverse pattern of gene expression when comparing AKI-recovery and AKI-fibrosis.

Conclusions: scRNAseq has enabled unbiased profiling of gene expression in disease states important in AKI-CKD. We have identified a novel mechanistic target which we are currently pursuing in knock-out gene experiments that impact macrophage phenotype, that we hypothesise, impacts recovery. This presents an exciting opportunity to study the mechanism of renal fibrosis following AKI.

Funding: Private Foundation Support
Methods: hPSC-derived kidney organoids were subject to repeated cisplatin injury twice weekly from differentiation days 49 to 63. Samples were harvested following each injury for immunostaining and qPCR to determine transition from intrinsic to incomplete repair. Single nuclear sequencing (snRNAseq) of pooled samples of control, intrinsic repair, and incomplete repair were compared to similar data sets of mouse UUO and IR, and renal window transplants. Transcriptomic results were validated with fibrotic human kidney biopsy samples by immunostaining. Targeted drug screening was conducted in kidney organoids to promote intrinsic repair for the identification of novel therapeutic candidates.

Results: snRNAseq from kidney organoids identified 159 differentially expressed genes and 29 altered signal pathways during intrinsic repair. Tabular atrophy and the induction of scar-forming myofibroblasts correlates with reduced expression of homology-directed repair genes in injured tubular cells, a finding supported by single cellular transcriptomics in models of obstructive, hemodynamic, and immune-mediated kidney injury, as well as biopsy samples of patients with fibrotic kidney disease. We identified FANC/D2/RAD51-mediated repair as a critical determinant governing the transition between intrinsic and incomplete repair and identified a novel therapeutic target for the prevention of CKD onset and progression following AKI.

Conclusion: Our findings demonstrate the utility of kidney organoids in determining novel pathologic pathways, conducting mechanistic studies of human kidney disease and identifying druggable targets through translational studies.

Funding: NIDDK Support, Other NIH Support - NIH DP2EB029388 award, NIH U10EB028899, NCATS UCALA CTSL KL2, Private Foundation Support

Acetylcholine Receptor Agonist Reduces Acute Lung Injury After Renal Ischemia-Reperfusion Injury by Acting on Splenic Macrophages


Background: Acute kidney injury (AKI) has been reported to contribute to development of acute lung injury (ALI) via proinflammatory response. Although the inflammation caused by AKI directly might affect the lungs, this inflammation has been exacerbated by splenectomy. Macrophages with α7 nicotinic acetylcholine receptor(α7nAChR), which play a central role in the cholinergic anti-inflammatory pathway (CAP), are abundant in the lung and spleen. We hypothesized that CAP could reduce ALI after AKI. The objectives of this study were to determine 1) whether AChR agonist could reduce ALI after AKI, and 2) which macrophages in the lung or spleen could contribute to the improvement of ALI after AKI.

Methods: AKI was induced in C57BL/6 male mice by unilateral ischemia-reperfusion injury (IRI) with contralateral nephrectomy. The α7nAChR selective agonist, GTS-21 was administered in the experimental settings: 1) spleenectomy, 2) splenic macrophage deletion via intravenous administration of clotrimazole liposomes, 3) alveolar macrophage deletion via intratracheal administration of clotrimazole liposomes. The lung neutrophil infiltration and Evans blue dye (EBD) leakage were assessed as lung injuries. Results: GTS-21 significantly reduced lung neutrophil infiltration (23.04±3.30 vs 11.69±2.38/HPF, p<0.001) and EBD vascular leakage (13.54±5.32 vs 8.04±5.25µg/g lung tissue, p<0.01) after renal IRI. In splenectomized mice, GTS-21 did not reduce lung injuries after renal IRI (neutrophil infiltration: 46.39±16.65 vs 35.74±12.91/HPF, p=ns, EBD vascular leakage: 23.30±8.88 vs 22.18±6.41µg/g lung tissue p=ns). In an intact model of splenic macrophages, GTS-21 did not reduced lung injuries after renal IRI/neutrophil infiltration: 37.03±1.54 vs 34.36±1.11/HPF, p=ns, EBD vascular leakage: 34.78±0.55 vs 49.92±3.85µg/g lung tissue, p=ns). In mice depleted of alveolar macrophages, GTS-21 significantly reduced lung injuries after IRI (neutrophil infiltration: 20.08±7.52 vs 11.3±3.03/HPF, p<0.05, EBD vascular leakage: 13.86±4.5 vs 9.74±2.25µg/g lung tissue, p=0.05).

Conclusions: AChR agonist reduces acute lung injury after renal IRI by acting on splenic macrophages.

T Cell Metabolic Reprogramming and Effect of Glutamine Blockade in Ischemic AKI


Background: T cells play an important role in the pathogenesis of AKI. Metabolic programming of T cells regulates T cell function, is a rapidly emerging field, and has not been studied in detail during AKI. We aimed to elucidate dynamics of T cell metabolism as well as the effect of blocking glutaminolysis on ischemic AKI.

Methods: We induced ischemic AKI with 30 min ischemia followed by reperfusion in C57Bl/6 mice and harvested kidneys and spleens at multiple early time points including during ischemia. Human nonischemic and ischemic kidney tissue was obtained from nephrectomy cases. T cells were isolated and analyzed by a flow cytometry-based immune-metabolic assay with interrogating metabolic programs. The data was evaluated by computational multidimensional analyses with machine learning. The glutamine antagonist JHU083, which targets T cell metabolism, was injected intraperitoneally and effects on AKI were evaluated.

Results: Unbiased high-dimensional analyses identified a distinct T cell subset with transcriptional activation of mitochondrial VDAC1 and phospho-S6 ribosomal protein (pS6) in postischemic kidneys. H3K27Me3 expression, regulated by TCA cycle, drove the segregation of ischemic kidney T cells from those of nonischemic kidneys in both humans and mice. Splenic T cells from post-AKI mice showed higher expression of GLUT1, hexokinase II (HKII), and CPT1α, indicating upregulation of glycolysis and fatty acid oxidation. Blocking glutamine uptake by JHU083 treatment attenuated renal injury at 24h (plasma creatinine 1.7±0.8 vs 1.0±0.5 mg/dl, P<0.03) and enhanced expression of pS6 (normalized MFI 0.38±0.07 vs 0.47±0.06, P<0.01) and HKII (0.31±0.04 vs 0.41±0.05, P<0.01) compared to vehicle-treated mice. Activation and proliferation were reduced in CD4+ (CD44, 61±7% vs 48±8%, P<0.05), CD8 T cells (CD44, 76±7% vs 55±11%, P<0.03) and CD8 T cells (CD44, 61±11 vs 41±11%, P=0.01; CD69, 25±7 vs 18±4%, P=0.02; Ki67, 61±13 vs 48±12%, P=0.04) but increased in double-negative T cells (CD44, 94±2 vs 96±1%, P=0.04; CD8, 72±7% vs 73%, P=0.01) and Ki67, 79±5% vs 91±3%, P=0.01) from post-AKI mice of the JHU083-treated group.

Conclusions: T cells undergo distinct metabolic reprogramming during ischemic AKI. Reconstitution of metabolism by targeting T cell glutamine pathway could be a promising therapeutic approach for AKI.

Funding: NIDDK Support
circBNC2 Inhibits Renal Fibrosis Through Regulating G2/M Cell Cycle

Methods: Unilateral ischemia reperfusion injury (IRI) was induced in mice by 25 min’s pedicle clamping. Organ harvest was taken from healthy state, day 1 (IRI-1D) and day 7 (IRI-7D) after IRI. Time point D0 represents healthy state.

Results: We identified one distinct subset among mononuclear phagocyte subsets according to the expression patterns of CD11b and CD11c in healthy kidney and lymphoid organs, of which IRF8 was significantly expressed in the CD11b+/CD11c- subset that mainly comprised cDC1s. Next, we applied a intravital deficient mouse line (Irrf8-/-Clec9a+/-) to specifically target Clec9a+ expressing cDC1s in vivo. During post-ischemic AKI/ADK, these mice lacked cDC1s in the kidney without affecting cDC2s. The absence of cDC1s mildly aggravated the loss of living primed tubule and decline of kidney function, which was associated with decreased anti-inflammatory Tregs-related immune responses, but increased T helper type 1 (Th1)-related and pro-inflammatory cytokines, infiltrating into tubules and acute tubule cell death, while we also observed a reduced number of cytotoxic CD8+ T cells in the kidney when cDC1s were absent.

Conclusions: Together, our data show that IRF8 is indispensable for kidney cDC1s. Kidney cDC1s mildly protect against post-ischemic AKI/ADK, probably via suppressing tissue inflammation and damage, which implies an immunoregulatory role for cDC1s.

Poster: Government Support - Non-U.S.

PO0398 Ischemia Reperfusion Activation of Kidney HDAC1 Results in Interstitial Fibrosis

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Background: Following a kidney ischemic event the chromatin remodeling enzyme, histone deacetylase-1 (HDAC1), is activated in many cell types of the kidney including fibroblasts/pericytes. Pharmacological inhibition of HDACs can attenuate ischemia-reperfusion-injury (IRI) mediated interstitial fibrosis. In this study, we tested the hypothesis that fibroblast/pericyte HDAC1 activation promotes interstitial fibrosis.

Methods: Tamoxifen inducible, fibroblast/pericyte HDAC1 knockout (KO) mice (HDAC1Cre+/-, Colla2-Cre) and littermate controls (HDAC1Cre-/-) were used. Male and female mice (8-10 wks of age) were given tamoxifen i.p. and IRI or sham surgery was performed after a 2-week tamoxifen washout period. A mild, 18 min, bilateral, warm IRI model was used and samples collected over 4 weeks. Additional groups of mice underwent unilateral ureteral obstruction (UUO) for 48 h. In vitro experiments with kidney fibroblasts cells (NRK-49F) overexpressing HDAC1 were used for RNA-seq-sequencing studies.

Results: HDAC1 KO was confirmed in myofibroblast cells by co-immunolocalization of HDAC1 and platelet-derived growth factor receptor beta or -smooth muscle actin (α-sma) in the kidneys of IRI mice. 24 h post ischemia there was a tripling of plasma creatinine (Pcr) in all IRI mice, regardless of sex or genotype. 2- and 4-weeks after IRI, Pcr were similar to sham values for all mice. However, the male control IRI mice had significant interstitial fibrosis but this was attenuated in the KO male IRI mice. The female mice, regardless of genotype, had very mild kidney damage and interstitial fibrosis at 4 weeks. The UUO male KO mice had reduced α-sma abundance compared to control male mice. Transcriptomes of NRK49F cells overexpressing HDAC1 had 15 genes upregulated (0.1% of the genes sequenced) and 64 genes downregulated (0.5%). Upregulated genes included C3, Bmp6, Ccl12, and Fzd1. Downregulated genes included Clec11b, Ifih1. Gene Ontology analysis determined significant enrichment in the regulation of Wnt signaling and innate immune response activating signal transduction.

Conclusions: For male and female tamoxifen-induced and tamoxifen/pericyte HDAC1 activation leads to pro-fibrotic programming of the myofibroblast and interstitial fibrosis. Future studies will determine the specific epigenetic pathways that may be significantly changed by HDAC1 activation leading to maladaptive interstitial fibrosis.

Funding: NIDDK Support

Poster: Government Support - Non-U.S.

PO0399 Endothelial and Not Proximal Tubule Epithelial Pannexin 1 Plays a Critical Role in Fibrosis Progression After AKI

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Background: Activation of pannexin-1 (Panx1) channels during acute kidney injury (AKI) and Panx1-mediated release of tissue messengers facilitates the recruitment and activation of immune cells to the site of injury. Lack of Panx1 in the proximal tubules (PT) or in the endothelial cells (EC) significantly reduces AKI. Metabolites released from Panx1 affect a number of biological processes that regulate inflammation and cellular metabolism. Thus, we investigated the role of PT or EC Panx1 during AKI to chronic kidney disease (AKI-CKD) transition by inducing deletion of Panx1 from PT or EC before or after an established AKI.

Methods: AKI was induced by unilateral ischemia-reperfusion injury (IRI), focal acid, or bilateral IRI. Cell-type specific deletion of Panx1 was achieved by injecting tamoxifen before or after AKI to Panx1 floxed (Panx1fl/+), animals expressing either PT (SLC34a4Cre+/-) (provided by B. Humphreys, University of Washington) or EC (Cdh5Cre+/-) specific inducible Cre-recombinase to generate either PT (SLC34a4Cre-Panx1) or EC

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167
increase of abundance of bacterial families of Sacccharimonas, Erysipelotrichaceae, Bacteroidoideae while decrease of Lachnospiraceae and Prevotellaceae were the hallmark of dysbiosis. Flow cytometry of gut immune cells showed a significantly increased percentage of IL-17A+/CD4+ cells in small intestine, whereas percent CD25+/CD4+ Tregs decreased significantly in colon, showing the gut immunity might also be involved in the development of AKI.

Conclusions: This is the first animal study that showed the development of structural brain injury and cognitive dysfunction long after AKI. Given that the important role of dysbiosis in various neurologic diseases, presence of dysbiosis and gut inflammation at time points long after AKI might contribute to the development of long-term neurologic sequela of AKI. Targeting the gut might be a novel therapeutic target for prevention of long-term adverse outcomes in AKI patients.

PO0402

Probiotics Supplementation Protects the Transition from AKI to CKD in Aged Mice via the Kidney-Gut Axis

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Background: Several epidemiological studies have reported that acute kidney injury (AKI) is more frequent in the elderly and they often progress to chronic kidney disease (CKD). Chronic inflammation has recently been reported as an important mechanism mediating CKD progression after AKI in the elderly. This study investigated how kidney and intestinal crosstalk is involved in exacerbation of inflammation in AKI and whether microbial targeted therapy could modulate the transition from AKI to CKD in aged mice.

Methods: In young and aged C57BL/6 mice, 25min bilateral ischemia reperfusion injury (IRI) was applied, and then colon inflammation, histological changes and intestinal barrier integrity were compared for 28 days post-IRI. To determine the role of the microbiome on kidney-gut crosstalk, we analyzed microbiome from feces in young and aged mice and examined the effects of probiotic supplementation.

Results: Aged mice was observed to have a higher incidence of AKI compared to young mice for 28 days after IRI. Interestingly, an intraluminal inflammatory milieu in aged mice was similarly observed in the colon on day 3 post IRI. The increased inflammatory cytokines in the colon were accompanied by an increase in TUNEL-positive apoptotic colonic epithelial cells, resulting in increased intestinal permeability in aged mice for 28 days. The AKI-induced “leaky gut” also showed a strong positive correlation with high TNF-α expression in mesenteric lymph nodes. Microbiome analysis revealed changes in Lactobacillus and Bifidobacterium in aged mice at the genus level. To confirm the role of the microbiome, probiotics were administered for 2 months during the AKI recovery period. We observed that administration of Bifidobacterium (B. longum + B. bifidum) altered intestinal Th1/Treg balance and improved kidney inflammation, but not intestinal leakage. They finally resulted in improvements in GFR and kidney fibrosis, suggesting that kidney-gut crosstalk in aged mice makes an important contribution to AKI to CKD transition.

Conclusions: Our study suggests that exacerbation of chronic inflammation through the kidney-gut axis is an important mediating mechanism of the transition from AKI to CKD in the elderly. Therefore, strategies to modulate the microbiota are considered promising to improve outcomes in elderly AKI.

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PO0403

The Proteomic Landscape of Liver After AKI

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Background: Acute kidney injury (AKI) was traditionally viewed as an "innocent bystander" in various critical illnesses that reflected disease severity in the clinic. Emerging evidence suggests that AKI is an independent protagonist that may cause acute diseases in other organs such as the liver. Thus far, the mechanisms of hepatic dysfunction in patients with AKI have not been well described. We have previously characterized the kidney proteome changes after septic AKI. Here, we further described the proteomic landscape of the liver and assessed the reno-hepatic communications after septic AKI.

Methods: Cecal ligation and puncture procedure was employed to construct the induced AKI model. Following AKI, the proteomic approach was applied.

Results: After septic AKI, alanine aminotransferase (ALT) levels were markedly induced in serum at day 2, while it then dropped, approaching the baseline at day 7. Significant process of liver damage and repair, PAS staining exhibited a consistent trend in liver morphological changes. To understand the molecular mechanisms in AKI-caused liver injury, we examined the global proteome and phosphoproteome of the liver on day 2 and day 7 after AKI using a recently developed ultrafast and economic filter-based sample preparation approach. We obtained a total of 1,673 proteins and 1,219 phosphoproteins in the liver. The principal component analyses indicated that the liver’s completely distinct protein expression patterns between day 2 and day 7 after AKI. The network analyses revealed that oxidation-reduction and metabolic processes are the top pathways in liver injury and repair. In the meantime, we identified a wide range of differential proteins in the liver after AKI, including Cyp7b1, cyp1l2, Hemopexin, Acss2, Oxml, Steap 4, and Haptoglobin. These proteins were further validated by western blot and immunostaining. Of particular interest, Steap4, a member of the six transmembrane epithelial antigen of the prostate, was significantly upregulated in the liver but not in the kidney upon septic AKI, suggesting a tissue-specific inflammatory response.
Conclusions: Our results imply that the liver's proteomic landscape after an IRI would be influenced by the remo-hepatic system and Steap4 may serve as a potential candidate to monitor AKI-caused liver injury in the clinic.

Funding: NIDDK Support

PO0404

COX-2-EP4-MafB Axes Protects Against Renal Fibrosis in Mice with Renal Ischemic Injury

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Background: The mammalian kidney is easily injured by ischemic or toxic insults but can often recover functional and structural integrity. Innate immunity is involved in both the injury and recovery processes, and its maladaptive response causes delayed recovery and development of kidney fibrosis. Cyclooxygenase 2 (COX-2) plays an essential role in antiinflammatory and tissue-reparative M2 polarization of macrophages, the major renal myeloid cells. Renal macrophage COX-2 increases after acute severe kidney injury (AKI). The current study investigated the role of renal macrophage COX-2 in ischemic AKI and subsequent development of fibrosis.

Methods: We developed myeloid COX-2-/- mice (CD11b-Cre; COX-2(-/-)), and myeloid MafB-/- mice (LysM-Cre; MafB-/-). We found that myeloid EP4 activation induced expression of MafB, a master transcription factor, to upregulate antiinflammatory genes and suppress proinflammatory genes in macrophages. Selective myeloid MafB deletion recapitulated the effects seen with myeloid COX-2-/- mice in response to ischemic AKI. We found that after a 2-h ischemic injury followed by reperfusion with renal pedicle clamping for 32 min. Results: Following ischemic AKI, COX-2 was selectively increased in renal macroporphages as indicated by colocalization with CD68, and myeloid COX-2-/- mice exhibited delayed renal recovery and increased tubulointerstitial fibrosis, in association with augmented proinflammatory cytokines in isolated renal macrophages. In bone marrow derived monocytes, PGE2 is the major COX-2-mediated arachidonic acid metabolites and acts primarily via EP4 receptors. Myeloid EP4-/- mice mimicked the effect seen with COX-2-/- mice in response to ischemic AKI. We found that myeloid EP4 activation induced expression of MafB, a master transcription factor, to upregulate antiinflammatory genes and suppress proinflammatory genes in macrophages. After 5 days of IRI, kidneys were collected for further analysis.

Conclusions: These studies show that COX-2-EP4-dependent MafB expression mediates renal macrophage antiinflammatory and pro-resolving polarization and identifies a potential target for therapeutic strategies to improve kidney recovery and chronic kidney injury, a finding that is relevant to understanding detrimental effects of NSAsIDs in the setting of renal dysfunction.

Funding: NIDDK Support

PO0405

Subcutaneous Adipose Stromal Cell-Derived Secretome Improves Renal Function and Fibrosis in Mice with Renal Ischemic Injury

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Background: Previous studies demonstrated that human adipose derived stem cells (ASC) attenuated the development of acute kidney injury (AKI) and preserved vascular density, when administered in the suprarenal aorta immediately following ischemia reperfusion (IRI). Recently, stem cell derived secretome, has received attention for the potential treatment of renal disease. We hypothesized that cell-free, concentrated fraction of ASC-derived secretome would improve renal function in a well-established rat model of AKI.

Methods: Male Sprague Dawley rats underwent bilateral IRI with 45-min of I/R to induce AKI. 24 hours later, renal function was evaluated (serum creatinine; SCR) and rats were randomized into vehicle or secretome-treated groups. Rats received subcutaneous (SQ) injection either secretome (2 mg/kg in 1 ml) or saline (1 ml) on day 1 and day 3 post IRI. After 5 days of IRI, kidneys were collected for further analysis.

Results: At 24 and post IRI, SCr levels were 3.3±0.2 mg/dl in vehicle treated rats and 3.3±0.2 mg/dl in secretome-treated rats (P=0.31). SCr level significantly (P=0.03) decreased in secretome treated ratscompared to the vehicle treated rats across 5 days study period. After 24 h administration of first secretome injection, there was a significant reduction of SCr level (27.8%, P<0.001) in secretome treated rats compared to their baseline. There was a significant increase of infiltration of dendritic/macrophage cells following IRI which was significantly reduced in secretome group (IRI; 1.2 X105 vs. control 1.0 X105) (P<0.05). Kidney tissue stained with periodic acid-Schiff reagent showed secretome treated improved the degree of tubular damage following IRI.

Conclusions: These data indicate that SQ injection of secretome following established AKI improves recovery and reduces infiltration of renal inflammatory cells. Thus, secretome might represent a useful option to treat AKI.

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PO0406

The Role of Disrupted Iron Metabolism in AKI: Targeting Iron Trafficking via the Hepcidin-Ferroportin Axis in Renal Proximal Tubules

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Background: Acute kidney injury (AKI) and iron-related disorders remain major clinical challenges associated with significant morbidity and mortality. Ferroportin (FPN) is an iron-exporter, identified as a modulator of iron balance. Hepcidin binds to FPN, causing its internalization and degradation. Though FPN and FPN are expressed in proximal tubule cells (PTCs) of the mouse kidney, their role in the pathogenesis of AKI is unclear. Through this work, we hope to determine if modulation of iron homeostasis by selective depletion of hepcidin or FPN in PTCs alters the response to AKI.

Methods: We generated PTCs-specific Hepcidin1 and Ferroportin (FPN) knockout (KO) by selectively expressing Cre in PTCs and confirmation with a red-green reporter (mTmG; Pepck-cre) allele. We subjected these mice to either the Folic Acid induced injury model, or the ischemia-reperfusion injury models of AKI. Serum samples were collected at 2, 7, 14, and 28 days after injury and BUN, creatinine, iron, and ferritin level were measured. Kidney tissues were collected at each time point for histology, iron deposition, immunohistochemistry, RNA isolation, and immunoblot analysis.

Results: Conditional KO mice were generated and deletion of Hepcidin1 and FPN specifically in PTCs was confirmed at the DNA and protein levels. Mutant young adult mice showed no gross morphology phenotype. However, both mutant strains developed pronounced iron deposition in PTCs measured with DAB-enhanced Perls stain for iron were significantly increased following increased ferroportin expression. After 2-h ischemic injury followed by reperfusion and regenerated damaged tubules leading worsening interstitial fibrosis, necrosis, and ferroptosis compared with wild type mice of the same genetic background. Markers of ferroptosis, fibrosis, and levels of ferritin will be quantified in serum and kidney tissue.

Conclusions: Our preliminary data indicate that disrupting iron trafficking in PTCs by manipulating the expression of FPN and hepatic decreases AKI severity and improves recovery. These findings may offer new insights into the role of iron metabolism in AKI and illuminate new therapeutic strategies for progressive kidney disease and other syndromes of iron overload.

PO0407

Noncanonical Wnt5a/CD146 Signaling Drives Renal Fibrosis by Activating Transcriptional Factor Snail in AKI

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Background: Acute kidney injury (AKI) with severe and persistent kidney cell injury will currently progress to permanent damage, progressive fibrosis, and chronic kidney disease (CKD). However, the exact cellular and molecular mechanisms mediating the progression of AKI to CKD remain incompletely understood. We recently reported that Wnt5a promotes renal tubular inflammation in diabetic nephropathy by binding to CD146 through noncanonical Wnt signaling. Snail, which expressed in the precursors of the renal epithelial cells, can induce partial epithelial-to-mesenchymal transition and drive renal fibrosis in mice. Here, we investigated whether modulation of Wnt5a expression during AKI would contribute to the progression to CKD.

Methods: To examine whether Wnt5a mediated cell migration during tubular injury model or the ischemia-reperfusion injury models of AKI. Serum samples were collected at 2, 5, and 28 days following injury. Using microarray analysis, we identified Wnt5a to further confirm the role of Wnt5a/CD146 signaling in the kidney injury. To examine whether Wnt5a/CD146/JNK pathway was involved in AKI, we determined the expression of Wnt5a and CD146 in the kidneys of AKI patients. Wnt5a knockdown mice underwent either unilateral ureteral obstruction (UO) or ischemia-reperfusion injury (IRI) to establish whether the loss of Wnt5a attenuated renal injury. In vitro, HK-2 proximal tubule cells were subjected to oxygen glucose deprivation (OGD) to mimic the ischemia-reperfusion injury. More over, HK-2 cells were transfected a wnt5a small interfering RNA (siRNA) to reduce the expression of Wnt5a to further confirm the role of Wnt5a/CD146 signaling in the kidney injury.

Results: Increased expression of Wnt5a and CD146 were found in the kidney sections of patients with AKI, which was associated with the severity of kidney injury and the progression to CKD. In an Wnt5a-knockdown mouse model subjected to UO or IRI, Wnt5a ablation significantly ameliorated kidney cell injury and renal fibrosis development. Mechanistically, Wnt5a promoted the phosphorylation of JNK and the activation of snail in UO and IRI models. Silencing Wnt5a with small interfering RNA (siRNA) attenuated the activation Wnt5a/CD146 signaling and the expression of snail in HK-2 cells with oxygen glucose deprivation (OGD). Our preliminary data indicate that noncanonical Wnt5a/CD146 signaling may be an important determinant in the severity of AKI. Through the activation of snail, it drives the renal fibrosis and promotes the progression to CKD.

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PO0408

Hyperactivation of CDK5 Promotes Proximal Tubule Cell Dedifferentiation and Intestinal Fibrosis in CKD

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Background: Chronic kidney disease (CKD) effects −15% of the world’s population. Recently, we demonstrated that Cyclin G1 (CG1) regulates proximal tubule cells (PTCs) G2/M arrest and promotes fibrosis. CG1 is known to act through Cyclin dependent kinase (CDK) 5, which regulates cell cycle exit and homeostasis in differentiated cells. Under

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Mechanistic Modeling of Kidney-Injury Molecule 1 (KIM-1) as a Biomarker for Cisplatin-Induced AKI

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DILysm Services Inc. A Simulations Plus Company, Research Triangle Park, NC.

Background: Kidney Injury Molecule 1 (KIM-1) is a specific and sensitive biomarker for drug-induced acute kidney injury (AKI) prediction. Cisplatin-induced injury of the renal proximal tubular epithelial cells (RPTEC) has been characterized using KIM-1 in in vitro studies. There is growing interest in clinical use of KIM-1 as a key biomarker for AKI diagnosis, a mechanistic model of KIM-1 that accurately predicts the kinetics of KIM-1 is still lacking. We developed a mechanistic model of KIM-1 as part of a quantitative systems toxicology (QST) model to predict urinary kidney KIM-1 in rats treated with cisplatin.

Methods: We developed a mechanistic model of KIM-1 within the framework of RENAsym, a QST model of drug-induced AKI that incorporates key cellular injury mechanisms and renal hemodynamics. The KIM-1 model represents the early shedding of KIM-1 arising from the loss of brush borders during sub-lethal injury of RPTEC followed by the expression of KIM-1 in differentiated cells in regenerating proximal tubules (Ichimura et al. 1998). The model is integrated with the RENAsym to capture RPTEC injury and regeneration following toxic renal injury.

Results: RENAsym was used to simulate the response of urinary kidney KIM-1 in rats treated with cisplatin. The model parameters were fitted to data from rats treated with 2.5 mg/kg cisplatin (Gebremich et al. 2017). The magnitude and time profile of KIM-1 were captured by the model. The KIM-1 model was also analyzed using data obtained from rats treated with single doses of 1mg/kg cisplatin, and it can recapitulate the dose-dependent responses of urinary kidney KIM-1.

Conclusions: Mechanistic model of KIM-1 was developed to quantitatively predicted cisplatin-induced AKI. The model recapitulated the urinary kidney KIM-1 data obtained from rats treated with cisplatin. Human data will be used in the future for model validation.

Funding: NIDDK Support

PO0412

The Role and Mechanism of DeR2-Positive Failed Repair Cells in AKI

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Background: Acute kidney injury (AKI) is a common clinical emergency and critical illness. The regeneration and repair of renal tubular cells determine the prognosis of AKI. Our previous study found that decay receptor 2 DeR2, a senescent marker, was specifically expressed in renal tubules and did not have the ability to proliferate in AKI, suggesting DeR2 may be associated with repair of tubular cells. This study aims to investigate the role and mechanism of DeR2-positive tubular cells in AKI.

Methods: The DeR2-GFP lineage trace mice, KSP-creDeR2f/f and GGT1-creDeR2f/f mice and Ischemia-Reperfusion (IR) Injury models were constructed. Confocal analysis the co-expression of DeR2-GFP and proximal tubular markers(AQP1, Villin), distal markers (AQP2), failed repair markers (Vcam1, Dcdc2), proliferative markers (Ki-67, Edu, PCNA), Ki1, differentiated markers (pax2, sox2, six2), senescent markers (P16, P21, SA-β-gal) and fibrotic markers (α-SMA, collagen I, Fibronectin). And wild type (WT) mice and DeR2 KO mice were used to compare the degree of renal tubules fibrotic damage and repair after IR injury. Furthermore, quantitative proteomics analyzed the downstream molecules of DeR2 in renal tissues from WT-AKI and CKO-AKI, and validated studies were done.

Results: The DeR2-GFP were mainly expressed proximal tubular cells in AKI. DeR2-GFP positive cells were co-expressed failed repair markers, such as senescent markers and co-localization with fibrotic markers. And DeR2-GFP positive cells were not expressed Ki1, proliferative and differentiated markers. The levels of Scr, BUN and renal injury scores were significantly lower in GGT1-creDeR2f/f than that of WT- KO. Moreover, the area of cell death and fibrotic tissue reduction was decreased. However, the above phenomenon of KSP-creDeR2f/f-AKI were not obviously improved. Additionally, quantitative proteomics and validated studies showed HMGC2S2, a key enzyme for Ketone Synthesis, was increased in GGT1-creDeR2f/f mice compared with WT-AKI. The levels of urine and serum β-hydroxybutyrate were higher in GGT1-creDeR2f/f mice.

Conclusions: Contrary to murine models, these results suggest severe defects in KIM-1-mediated phagocytosis do not predispose to acute kidney dysfunction after IR injury in humans.

Funding: Government Support - Non-U.S.
Conclusions: DeR2-positive tubules were failed-repair cells in AKI. And DeR2 promoted failed repair of tubular cells through regulating the expression of HMGCS2 thus affects the metabolism of β-hydroxybutyrate, suggesting that DeR2 may be a potential intervention target during the progression of AKI.

Funding: Government Support - Non-U.S.

PO0413 Mini-Pulse and Fast-Tapering Corticosteroids in Acute Tubulointerstitial Nephritis Related to Immune Checkpoint Inhibitors: Testing a Treatment Scheme Raquel B. Rico, Hospital Universitario 12 de Octubre, Madrid, Spain.

Background: Acute tubulointerstitial nephritis (ATIN) is the most common lesion seen on kidney biopsy related to immune check-point inhibitors (ICI) in oncological patients. Clinical and laboratory features as well as risk factors are well known, albeit non-specific in predicting the underlying renal lesion. Corticosteroid-based therapy has proved to be effective, however, the optimal duration of treatment has not yet been established.

Methods: We conducted a retrospective single-center study to evaluate a treatment scheme with low-dose corticosteroids in patients diagnosed with ATIN between 2017-2021. Extrapolating our treatment scheme for acute interstitial nephritis, we administer pulses of methylprednisolone (2 mg/kg/day for 3 consecutive days) followed by prednisone 1mg/kg/day with rapid-tapering until total withdrawal 2 months after treatment onset. The main outcome was immune response during follow-up.

Results: We included a total of 8 patients (87.5% males) with a median age of 66.5 years and diagnosis of metastatic disease in all cases. Three patients had uraemic cancer, two had renal cell carcinoma and lung cancer, and one had hepatocellular carcinoma. Moreover, 3 patients had already been treated with PDE-1 and PDI-1 inhibitors and employed in 62.5 and 37.5% of the cases, respectively. Baseline serum creatinine (Scr) was 1.1 mg/dl (0.8-1.5), three patients had chronic kidney disease and six patients were on treatment with proton pump inhibitors. Acute kidney injury presented 13.5 weeks after starting ICI therapy. The median highest Scr was 3.2 mg/dl (2.5-3.5) and one patient required acute dialysis. Urinalysis alterations were present in all patients (proteinuria in 50%, hematuria in 75%, and sterile pyuria in 87.5%). Complete renal response was observed in all cases, except for one patient who showed a partial response. ICI rechallenge was not applied to any patient and no ATIN recurrences were documented after corticosteroids discontinuation. Two patients died due to oncologic disease progression. Median follow-up was 12.5 months (2.5-27.5).

Conclusions: Our treatment scheme with fast-tapering corticosteroids was effective for inducing renal response in ICI-related ATIN, without evidence of relapses.

PO0414 Contralateral Nephrectomy Stimulates Proliferation of Renal Epithelial Progenitor Cells After Unilateral Ischemia Lies Moonen,1 Elena Lazzi,2 Anna J. Peird,2 Carolina Conte,2 Paola Romagnani,2 Patrick D’Haese,1 Benjamin A. Vervaat,1 Laboratory of Pathophysiology,1 Universiteit Antwerpen Laboratorium voor Pathofysiologie, Wilrijk, Belgium; 2Universita degli Studi di Firenze Dipartimento di Scienze Biomediche Sperimentali e ClinicheMario Serio, Firenze, Italy.

Background: Acute kidney injury is a global health concern and important risk factor for the development of chronic kidney disease. Crucial for successful renal recovery after AKI is the proliferation of surviving tubular epithelial cells. We established a murine model in which functional and histological recovery of a kidney, injured by ischemia, is enhanced by removal of the contralateral kidney, i.e. nephrectomy-induced recovery. The epithelial reparative response in this unique model has not been investigated, yet can provide new insights in the inherent regenerative potential of the renal epithelium.

Methods: AKI was induced in two different mouse strains by left unilateral ischemia/reperfusion (UIR) after which either right nephrectomy (Nx) or no Nx was performed on day 3. In R26RtdTomato mice kidney-to-body-weight ratio, renal function (serum creatinine) and histology were measured at day 6. Additionally, renal tissue of PAX2/Confetti mice was processed to study clonal expansion by lineage pattern analysis of PAX2+ renal epithelial progenitor cells at day 28.

Results: When no Nx was performed after UIR, a significant decrease in left kidney-to-body weight ratio along with increased fibrosis and functional loss were observed in the injured kidney at week 6 compared to controls. However, when Nx was performed, renal function and mass were preserved. During spontaneous repair after UIR (i.e. without Nx) clonal analysis in PAX2/Confetti mice revealed a significant increase in clone size frequency from mainly monoclonal PAX2+ progenitor cells in controls to an increased number of multiclonal clones. When Nx was performed after UIR, this clonal expansion was further significantly stimulated. Likewise, the percentage of PAX2+ cells stimulated to divide (i.e. clonogenicity) was significantly higher when Nx was performed after UIR (42%) as compared to when no Nx was performed (28%).

Conclusions: Nx overcomes loss of renal mass and function after UIR. This enhanced recovery is at least established by increased clonogenicity and enhanced clonal expansion of renal progenitor cells that surpasses that of spontaneous repair after UIR. Getting insight in the signaling mechanisms by which nephrectomy achieves this response may open new therapeutic research avenues.

PO0415 Long Noncoding RNA Neat1 Promotes Tubular Epithelial Cells Apoptosis to Facilitate the Progression of AKI to CKD Tongtong Ma,1 Peng Wang,2 Department of Critical Care Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, China; Division of Nephrology, Nanfang Hospital, Southern Medical University, State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Guangzhou, China.

Background: The severity and frequency of acute kidney injury (AKI) determine if the injury leads to chronic kidney disease (CKD). A growing number of research shows that the injury of tubular epithelial cells (TECs) is the driving force during chronic progression of AKI. However, there are limited knowledge about the role of lncRNAs in the progression of AKI.

Methods: To screen out the candidate IncRNA in the progression of AKI to CKD, 8-week old C57BL/6 mice were subjected to mild-AKI (20 min-ischemic reperfusion injury) and severely-AKI (40 min- ischemic reperfusion injury). RNA-sequencing was performed with the isolated tubules from mild- or severe-AKI mouse. The expression of a candidate IncRNA Neat1 was evaluated by FISH, Northern blot and real-time qRT-PCR in HK2 cells and mouse kidney tissues. To study the biological function of Neat1 in vitro, CRISPR-Cas9 was used to knock out Neat1, while Neat1 was ectopic overexpressed by lentivirus. HK2 cells were cultured in anoxic environment as the in vivo model to study the function of Neat1. RNA pull down was performed to screen out the microRNAs that bound to Neat1. Knocking down Neat1 in vivo was performed by injecting Adeno-associated virus serotype 9 (AAV9) particles carrying siRNA targeting Neat1. Flow cytometer was used to calculate the apoptotic cells under each treatment. TUNEL was applied to evaluate the apoptotic TECs in kidney sections.

Results: The expression of Neat1 was upregulated in the tubules from severe AKI mouse, as compared to mild AKI mouse. Knocking out Neat1 inhibited hypoxia-induced HK2 cells apoptosis while overexpression of Neat1 enhanced the apoptosis of HK2 cells in vitro. Furthermore, knockdown of Neat1 in vivo reduced the apoptosis of TECs and improved the kidney functions of IRI mice.

Conclusions: Our results showed that LncRNA neat1 regulated apoptosis of TECs and might be served as a therapeutic target to ameliorate AKI.

Funding: Government Support - Non-U.S.

PO0416 Effects of Proton Pump Inhibitors (PPIs) on Renal Vasoreactivity in Cirrhotic Rats Chiao-Lin Chiang,1 2Taipei Veterans General Hospital, Taipei, Taiwan; 2National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan.

Background: Hepatorenal syndrome is, a lethal complication of cirrhosis, defined as renal hypoperfusion resulting from intense renal vasconstriction. Vascular dysregulation such as ET-1 and nitric oxide (NO) might be the contributing factor. Proton pump inhibitors (PPIs) are widely used for peptic ulcer. Although generally safe, recent studies reported that PPIs decreased NO production, leading to reduction of arterial relaxation. The prevalence of gastric ulcer in cirrhotic patients is higher than healthy controls. The impact of PPIs on renal vasoreactivity in cirrhosis is worth to be studied.

Methods: Liver cirrhosis was induced in S-D rats by common bile duct ligation (CBDL). Sham-operated (SHAM) rats were surgical controls. On the 29th day after surgery, in-situ renal perfusion was performed. In acute treatment study, rats were randomly assigned to receive Krebs solution or Esomprazole (30 mcm) incubation for 1h before renal perfusion. In chronic treatment study, rats were randomly received oral distill water or Esomprazole (3.6 mg/kg/d) for 28 days.

Results: The were no significant changes in renal vascular reactivity to ET-1 after acute (Fig A) and chronic (Fig B) PPIs treatment in CBDL rats. Chronic PPIs treatment had no significant effects on systemic hemodynamics and renal function but decreased hemoglobin in both SHAM and CBDL rats (Table).

Conclusions: In conclusion, PPIs showed no renal vascular effects. The mechanisms of lower hemoglobin following PPIs treatment need further analysis.

Table. Hemodynamic and biochemistry data

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Mean arterial pressure 0 (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM</td>
<td>146±15</td>
<td>135±15</td>
<td>357±17</td>
<td>133±15</td>
</tr>
<tr>
<td>CBDL</td>
<td>159±15</td>
<td>145±15</td>
<td>381±17</td>
<td>138±15</td>
</tr>
</tbody>
</table>

Conclusions:

¶, P < 0.01 vs SHAM group
‡, P < 0.01 vs chronic PPIs-treated group

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO0417**

**Hospitalized AKI Is Associated with Long-Term Increases in TNFR1 and TNFR2: Findings from the CRIC Study**

Ian Mccoy,1 Jesse Y. Hsu,2 Joseph V. Bonventre,3 Chirag R. Parikh,4 Chi-yuan Hsu,1 University of California San Francisco, San Francisco, CA; 2University of Pennsylvania, Philadelphia, PA; 3Brigham and Women’s Hospital, Boston, MA; 4Johns Hopkins University, Baltimore, MD.

**Background:** Evaluation of plasma biomarkers before and after AKI may yield valuable insights into the pathogenesis of progressive CKD after AKI. Markers of endothelial inflammation and injury, Tumor Necrosis Factor Receptors 1 and 2 (TNFR1 and TNFR2), are associated with progressive CKD, but it is unknown whether an episode of hospitalized AKI may cause long-term changes in these biomarkers.

**Methods:** Among participants in the prospective Chronic Renal Insufficiency Cohort (CRIC), episodes of hospitalized AKI were identified using acute changes in inpatient serum creatinine levels (peak nadir ≥ 1.5). For each AKI hospitalization, we found the best matched non-AKI hospitalization (unique patients) using the following pre-hospitalization criteria: estimated glomerular filtration rate (eGFR), urine protein/creatinine ratio, duration between hospital discharge and next CRIC visit (max 1 year), diabetes, age, sex, and duration between hospital admission and prior CRIC visit (max 2 years). We measured plasma levels of TNFR1 and TNFR2 using banked plasma samples collected at CRIC study visits before and after the hospitalization. Biomarkers were measured using a customized U-Plex assay on a MesoScale Device.

**Results:** Study participants who did and did not have AKI were well matched (Table). Pre-hospitalization TNFR1 and TNFR2 levels were also similar. AKI was associated with greater increases in TNFR1 (p<0.01) and TNFR2 (p<0.01).

**Conclusions:** Hospitalized AKI was associated with increases in plasma TNFR1 and TNFR2 months after the hospitalization.

**Funding:** NIDDK Support

*P < 0.05 comparing AKI vs. non-AKI.

**PO0418**

**Can Urinary Biomarkers at AKI Predict Progression to CKD?**

Jennifer R. Charlton,1 Teng Li,1;2 Yanzhe Xu,1,2 Teresa Wu,3 Kimberly Deronde,1 Kevin M. Bennett,4 University of Virginia School of Medicine, Charlottesville, VA; 1,2 Arizona State University, Tempe, AZ; 3Arizona State University-Mayo Center for Innovative Imaging, Tempe, AZ; 4Washington University in St Louis, St Louis, MO.

**Background:** Acute kidney injury (AKI) can cause permanent structural changes and progressive chronic kidney disease (CKD). If kidney function normalizes after AKI, it is difficult to distinguish who will progress to CKD. We evaluated urinary biomarkers from mice at the time of AKI and correlated them to a range of structural features derived from histopathology and cationic ferritin enhanced-MRI (CFE-MRI) in the kidney later in life. We investigated whether these biomarkers at AKI could predict future progression to CKD.

**Methods:** Adult male mice were injected with folic acid (AKI) or NaHCO3 (controls), (n=8/group) and urine was collected after 4 days. Biomarkers were measured using the CytoLex Array Q1000 (Ray BioTech). Mice received CF 12 wks after AKI and kidneys were imaged ex vivo using a 7T MRI. Structural metrics were derived by CFE-MRI (N0 and vTmax) and histology (proximal tubule (PT) content, atubular glomeruli (ATG), and scarred area).

**Results:** We performed a univariate analysis comparing the AKI and controls. Using hierarchical edge bundling, there were 19 connections between the urinary biomarkers and structural metrics at 12 wks and 7 connections in the control group (Fig 1A). EGF, OPG, TARC and TNF RII (correlation r=0.8, Fig 1B) were correlated to structural metrics in AKI and only IGFBP-6 was correlated to the structural metrics in controls. We developed predictive models using the 13 urinary biomarkers in Fig 1B. The best model predicted mean ΔN0 (r=0.67), %ATG (r=-0.50) and PT content (r=-0.47).

**Conclusions:** Urinary biomarkers, alone or in combination, may provide noninvasive predictive markers for progression to CKD after AKI. We identified 13 urinary biomarkers that appear to predict structural changes in the kidney 12 weeks after AKI and may serve as candidate biomarkers to predict outcomes in patients.

**Funding:** NIDDK Support

**PO0419**

**The Kidney Produces a Non-Polymerizing Form of Uromodulin That Associates with Reduced Risk of AKI**

Radmila Micanovic, Kaise A. LaFavers, Kavish R. Patidar, Shehnaz Khan, Tarek M. El-Achkar. Indiana University School of Medicine, Indianapolis, IN.

**Background:** Uromodulin (Tamm-Horsfall protein, THP) is a glycoprotein uniquely produced in the kidney. It is released by cells of the thick ascending limbs (TAL) apically in the urine, and basolaterally in the renal interstitium and systemic circulation. Processing of mature urinary THP, which polymerizes into supra-molecular filaments, requires cleavage of an external hydrophobic patch (EHP) at the C terminus. However, THP in the circulation is not polymerized, and it remains unclear if non-aggregated forms of THP exist natively in the urine. We propose that an alternative processing path, which retains the EHP domain, can lead to a non-polymerizing form of THP.

**Methods:** We have generated an antibody that specifically recognizes THP with retained EHP (THP+EHP). Liquid chromatography, mass spectrometry and C terminal sequencing were performed to delineate potential sites of enzymatic cleavage of immunoprecipitated THP+EHP. Immunofluorescence confocal microscopy was used to localize this isopform in the human kidney. Finally, we finally developed a customized ELISA to measure THP+EHP and used it on urine and plasma samples from a small cohort of patients hospitalized with liver cirrhosis.

**Results:** Using native and denaturing Western blots, we established the presence of THP+EHP in a non-polymerized native state. Proteomic studies confirmed the identity of THP+EHP and suggested that enzymatic cleavage occurred at Arg615, which is one amino acid beyond the GPI anchoring site. In the human kidney, THP+EHP predominantly co-localized with urinary THP in TAL cells, but it was also detected, at lower levels, in other tubular segments. In a cohort of patients with liver disease, admission urinary THP+EHP, but not total THP was significantly lower in patients who subsequently developed acute kidney injury during hospitalization. THP+EHP was also detected in the plasma, albeit at very low concentrations.

**Conclusions:** Our findings uncover novel insights into uromodulin biology by establishing the presence of an alternative path for cellular processing. Our proof-of-principle findings in patients warrant further investigations to establish the utility of THP+EHP as a sensitive biomarker of kidney health and susceptibility to injury.

**Funding:** NIDDK Support, Veterans Affairs Support

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

Underline represents presenting author.
Aggravate renal ischemia/reperfusion (I/R) injury in mice.

Background: The biggest city in Latin America is São Paulo (SP), where disorganized urbanization has had a negative impact on air quality and vehicle emissions are the main source of fine particulate matter (PM$_1$. Epidemiological studies have linked PM$_1$ exposure to an increased risk of I/R. The mechanisms mediating the adverse health effects of PM$_1$ include epigenetic changes, oxidative stress and inflammation. The role of PM$_1$ in AKI has yet to be described. We hypothesized that PM$_1$ exposure would aggravate renal ischemia/reperfusion (I/R) injury in mice.

Methods: In temperature-humidity-controlled chambers within an ambient particle concentration, animals were exposed to a concentrated PM$_1$ stream (PM$_1$) or to high-efficiency particulate air-filtered clean air (CA). Mass concentrations of PM$_1$ were measured with an airborne particulate monitor, and the target dose was 600 µg m$^{-3}$ (equivalent of the daily exposure in SP). After 12 weeks, some PM$_1$ and CA mice underwent unilateral 30-min clamping of the kidney hilum and subsequent reperfusion. All studies were performed 48 h after I/R. Groups: CA, PM$_1$, CA+I/R and PM$_1$+I/R. Data are means±SEM.

Results: Renal TLR4 protein expression was higher in CA+I/R and PM$_1$+I/R than in CA and PM$_1$(128±2.1 and 146±2.0 vs. 97±2.1 and 98±0.9%; P<0.05), also being much higher in PM$_1$+I/R than in CA+I/R (P<0.05). Manganese superoxide dismutase levels were higher in PM$_1$+I/R than in CA+I/R, AF and PM$_1$(164±12 vs. 99±3.6, 102±3.9 and 96±2.8; P<0.05).

Conclusions: PM$_1$ aggravates I/R-induced AKI by decreasing renal Klotho protein, leading to increased renal TLR4 expression and inflammatory cell infiltration. (FAPESP, NWO)

Funding: Government Support - Non-U.S.

Biochemistry and histology

*Immunohistochemical analysis; P<0.05 vs. CA, PM$_2$.5 and CA+I/R; P<0.05 vs. CA and PM$_2$.5.

**Proteogenomic Effects of Environmental and Uremic Toxin Acrolein on Mouse Kidneys**

Sanjana Rane, Shunying Jin, Susan M. Isaacs, Michelle T. Barati, Michael Merchant, Jianmin Pan, Shesh Rai, Sanjay Srivastava, Madhavi J. Rane. University of Louisville, Louisville, KY.

Background: Acrolein is present in the environment, water, food, and is a toxic endogenously produced lipid peroxidation and polynuclear oxidation. Its mechanism of action involves cellular thiol reactivity and glutathione depletion-induced oxidative stress. However, direct effects of acrolein on kidneys are not known. The current study conducted RNA-seq and proteomic analysis on mouse kidneys exposed to acrolein.

Methods: C57BL/6 mice were subjected to filtered-air (control) or inhaled-acrolein (1.0 ppm), 6h/day, 5 days/week for 12 weeks. Total-RNA and kidney homogenates from all mice were subjected to RNA-seq and proteomic analysis. Immunoblotting, H&E and Sirius-Red staining of kidneys was performed.

Results: RNA-seq analysis detected activation of profibrotic pathways including CTGF expression and caspase-3 cleavage. Collagen deposition in kidneys of acrolein exposed mice. Over-expression of NF-E2 in caspase-3 and profibrotic connective tissue growth factor (CTGF) expression. H&E decreased expression of antioxidant proteins, non-erythroid hemoglobin and glutathione apoptosis, and inflammatory pathways. Proteomic analysis demonstrated acrolein-activation of oxidative stress, mitochondrial dysfunction, proteasomal degradation, and inflammatory pathways. Proteinomic analysis demonstrated acrolein-decreased expression of antioxidant proteins, non-erythroid hemoglobin and glutathione synthetase (GSS), targets of transcription factor Nuclear Factor-Erythroid derived-2 (NRF-2). Accordingly, acrolein decreased renal NF-E2 expression and increased cleaved caspase-3 and profibrotic connective tissue growth factor (CTGF) expression. H&E staining demonstrated damaged tubules while Sirius-Red staining demonstrated increased collagen deposition in kidneys of acrolein exposed mice. Over-expression of NF-E2 in immortalized human renal proximal tubule (HRK-11) cells, inhibited acrolein-induced CTGF expression and caspase-3 cleavage.

Conclusions: Our studies demonstrate activation of oxidative stress, apoptotic and profibrotic pathways in acrolein treated kidneys. Chronic exposure of acrolein may lead to progressive fibrosis-induced End Stage Renal Disease (ESRD). In vivo modulation of NF-E2 expression may slow-down progressive fibrosis-induced ESRD.

Funding: Other NIH Support - NHI/NEHS P30 ES030283

**Impaired Renal Hemodynamic Reserve Following Ischemic AKI Is Associated with Inflammation and Capillary Rarefaction and Reversed by Retrograde Hydrodynamic Isotonic Fluid Delivery**

Md Mahbub Ullah, Jason A. Collett, Robert L. Bacallao, David P. Basile. Indiana University School of Medicine, Indianapolis, IN.

Background: We have previously shown that retrograde hydrodynamic delivery of isotonic fluid (HIFD) improved renal function in established AKI between 24-48 hours following ischemia and reperfusion injury (IRI). This improvement was associated with decreased inflammation and vascular congestion and improved microvascular perfusion. However, it is unknown whether HIFD results in sustained effects on renal hemodynamic reserve and CKD progression.

Methods: Male Sprague Dawley rats underwent unilateral left renal IRI-35 min with right unilateral nephrectomy to induce AKI. 24 hours later, serum creatinine (SCre) was measured and rats received either HIFD via the renal vein or 0.5ml of isotonic saline into the vena cava (VC) as control. After 5 weeks, renal hemodynamic responses were assessed in response to i.v. L-arginine infusion (450 mg/kg/hr) in anesthetized rats. Kidneys were evaluated for further analysis.

Results: At 5 weeks of recovery from surgery, baseline renal blood flow (RBF) and renal vascular resistance (RVR) were similar in the experimental groups (sham-, HIFD-, and VC-treated rats). Following 40 minutes of arginine infusion RBF increased similarly in both the sham group and the IR I/R HIFD group (22.6% and 19.8% compared to their corresponding baseline value (P<0.001). However, IR/VC treated rats showed an impaired response to arginine infusion relative to the sham group (P<0.001). As expected, RVR to blood flow was decreased significantly by 14% and 17% in sham operated and HIFD treated rats compared to their corresponding baseline respectively. In the kidney, HIFD treatment attenuated recruitment of inflammatory CD4+IL17^+ cells (777±69 vs. 417±60, p<0.05), as assessed by flow cytometry compared to the VC-treated rats. Perturbative capillary density in medulla, measured by cablin immunofluorescence, was significantly reduced by (41%) in VC-treated rats compared to sham group. HIFD treatment significantly improved capillary density after 35 days of IRI.

Conclusions: HIFD treatment showed improved impaired renal blood flow response to arginine infusion following 35 days IRI. This is associated with improved capillary density and attenuated infiltration of CD4+IL17^+ cells. This data shows that HIFD treatment has long-term protective effects following I/R injury.

Funding: NIDDK Support, Veterans Affairs Support

**Evidence for a Critical Role of ARNT Homodimerization in Renal Regeneration and Attenuation of Fibrosis**

Michael Zeisberg, Bjoern Tappe. Georg-August-Universitat Gottingen, Gottingen, Germany.

Background: Based on the organ-spanning effectiveness of ischemic preconditioning we hypothesized that underlying mechanisms could be utilized to aid the kidney in regenerating and to protect it from acquiring or progressing fibrosis. Previous studies implied that ARNT, also known as HIF1beta, plays an important role independent of HIF1alpha in ischemic preconditioning. Here we aimed to explore the mechanisms underlying the renoprotective activity of ARNT and to exploit these mechanistic insights for novel therapeutic strategies.

Methods: ARNT homodimerization in vivo and in vitro was studied by mass spectrometry, immunoprecipitation, proximity ligation assays, native gel analysis and the use of mutant ARNT variants. Control of ARNT expression was studies by use of qRT PCR, immunoblot and promoter assays. To study impact of ARNT homodimerization in vivo we utilized murine models of UU and CC4-induced liver fibrosis.

Results: We provide evidence that transcriptional induction of ARNT by administration of FK506 or Tacrolimus enhances renal regeneration and attenuates renal fibrosis in vivo. This effect is not realized when ARNT is only Realized when it forms homodimers. ARNT homodimers acts as transcription factor on ALK3 and the protective effect of ARNT homodimers is not realized when ALK3 is lacking. We identify that ARNT dimerization decision to form homodimers is controlled by phosphorylation of a critical serine 77 amino acid. ARNT Ser77 phosphorylation is lacking. We identify that ARNT dimerization decision to form homodimers is controlled by phosphorylation of a critical serine 77 amino acid. ARNT Ser77 phosphorylation is controlled by PP2A. The PP2A inhibitor LB100 enhances Ser77 phosphorylation, ARNT homodimer formation and attenuates fibrosis in the kidney. Combination of GP11046 (to induce ARNT transcription) and LB100 (to enhance ARNT homodimers) has additive effect to protect against fibrosis in kidney and liver.

Conclusions: Increased intracellular ARNT levels through enhanced transcription and augmented homodimerization through phosphorylation of ARNT Ser77 are prerequisites to realize the renoprotective activity of ARNT. Utilization of this dual mechanism through combination therapy has potential to protect the kidney.
PO0424
TGF-β1-Mediated Tubular Injury and Cell Death Requires Recruitment of Inflammatory Cells via CCL5
Emelie Lassen,1 Liping Yu,1 Kristzian Stadler,2 Ilse S. Daehn,1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Pennington Biomedical Research Center, Baton Rouge, LA.
Background: Activation of the TGFβ signaling pathway plays an important role in both AKI and CKD pathogenesis. We have previously shown that ligand-independent activation of TGFβ1 in proximal tubular cell tubules results in rapid epithelial cell injury and death, as well as immune cell infiltration. This study aims to determine the drivers and mechanism of epithelial cell injury.
Methods: In vivo studies were performed in transgenic Pax8Tgfb1 mice with proximal tubular activation of TGFβ1 signaling by +/- doxycycline (Dox) show. Immortalized proximal tubular epithelial cells (PTECs) from Pax8Tgfb1 mice were treated with Dox and with activated spleen derived leukocytes. Cell death was determined by TUNEL or AnnexinV/PI staining, lipid-derived free radicals by electron paramagnetic resonance (EPR) spin resonance spectroscopy and in vivo spin trapping, and mitochondrial superoxide was determined by mitoSOX. Gene and protein expression were determined by RT-PCR, western blotting and immunofluorescence.
Results: Canional TGFβ signaling induced by Dox was confirmed in Pax8Tgfb1 mice and in isolated PTECs by decreased expression and phosphorylated SMAD2 or nuclear translocation of SMAD2/3. Markers of tubular cell injury and inflammation were prominent in kidney sections from Pax8Tgfb1 mice after 5 days of Dox. There was also increased oxidative stress and cell death after 5 days. TGFβ1 signaling antagonized in cultured Pax8Tgfb1 PTECs did not induce cell death, but showed an increase in CCL5/RANTES expression, a chemokine involved in recruitment of several immune cell types, among them monocytes and T-cells. PTECs co-cultured with leukocytes isolated from spleens resulted in mitochondrial oxidative stress and cell death of PTECs. Cell death and mitochondrial oxidative stress was ameliorated by a mitochondrial superoxide scavenger determined to be mitoSOX. Gene and protein expression were determined by RT-PCR, western blotting and immunofluorescence.
Conclusions: These studies show that induction of TGFβ1 signaling in tubular epithelial cells triggers recruitment of inflammatory cells which mediate mitochondrial stress and cell death.
Funding: Other NIH Support - NIH grant R01DK097253

PO0425
Kidney-Draining Lymph Node Fibrosis Following Unilateral Ureteral Obstruction
Xiaofei Li1, Jing Zhao,1 Stefan G. Tullius,1 Su Ryon Shin,1 Jonathan Bromberg,2 Vivek Kasinath,3 Reza Abdi,1* 1Brigham and Women's Hospital, Boston, MA; 2University of Maryland School of Medicine, Baltimore, MD.
Background: Although the primary organ has been the subject of intense investigation in the field of organ fibrosis over the past several decades, the presence of lymph node fibrosis due to persistent activation of the immune response in its partner organ remains largely unknown. Previously, we demonstrated that activation of the immune response following ischemia-reperfusion injury and crescentic glomerulonephritis in the kidney was associated with extracellular matrix (ECM) production by fibroblastic reticular cells (FRCs) of the kidney-draining lymph node (KLN). Here, we sought to determine whether FRCs in the KLN become similarly fibrogenic following unilateral ureteral obstruction (UUO) of the kidney.
Methods: We subjected 6–8-week-old C57BL/6J mice to UUO for 2, 7, and 14 days. We examined the microarchitecture of the kidney and KLN by immunofluorescence staining at each timepoint, and we quantified immune cell populations in the KLN by flow cytometry. The contralateral kidney unaffected by UUO and its partner KLN were used as controls.
Results: We found immunofluorescence staining that FRCs’ increased production of ECM fibers and remodeled the microarchitecture of the UUO KLN, possibly via angiogenesis. First, we comprehensively preconditioning (RIP) in mice, possibly via angiogenesis. First, we comprehensively
Conclusions: Our studies show that induction of TGFβ signaling in tubular epithelial cells triggers recruitment of inflammatory cells which mediate mitochondrial stress and cell death.
Funding: Other NIH Support - NIH grant R01DK097253

PO0426
The Irradiation-Induced Renal Inflammatory Preconditioning Is Blunted by the Oral Administration of the Anti-Inflammatory Agent Sunitinib
Bouchart-Bastard,1 François Lallemand,1 Pompa Laurence,1 Jean-Marie H. Krezeski,1 François Jouret,1 Laboratory of Translational Research in Nephrology (LTRN) - GIGA Institute 1Université de Liège Faculté de Médecine, Liège, Belgium; 2University of Pittsburgh Medical Center, Pittsburgh, PA.
Background: Whole-body irradiation has been suggested to induce renal inflammatory preconditioning (RIP), in mice, possibly via angioinvasion. First, we comprehensively investigated the pathways involved in renal irradiation. Next, we assess the functional impact of renal irradiation applied before renal ischemia/reperfusion (IR) injury. Finally, we test whether Sunitinib-mediated inhibition of the angiogenesis prevents irradiation-associated RIP.
Methods: Exp1: Renal irradiation(8.56 Gy) was performed in male C57bl/6 mice(n=10). One month later, total kidney RNA was extracted from irradiated and control(n=5) mice for comparative RNA-Seq. Exp2: After renal irradiation, the right kidney was removed, and the left kidney underwent ischemia(30min)/reperfusion(4h) at Days 7-14-28 post irradiation(n=8). Exp3: Following the same protocol of I/R at Day14, 3 groups were compared(n=8): 1) irradiation; 2) irradiation and gavage with Sunitinib from Day2 to 13; 3) control group without irradiation or gavage.
Results: Exp1: RNAseq analysis of angiogenesis signalling pathways. Expressions of angiogenesis markers(CD31, VEGF) showed an increase at both mRNA and protein levels in irradiated kidneys(p<0.01). Exp2: Following I/R, Blood Urea Nitrogen(BUN) and Creatinine(SCr) levels were lower in the irradiated mice compared to controls: BUN: 86.2±8.8 vs. 454.5±227.9mg/dl; SCr: 0.16±0.01 vs. 1.7±0.2mg/dl( p<0.01). The renal inflation by CD11b(187a±32 vs 477±20mm²) and F4-80-positive cells(110±22 vs 212±25mm²) was reduced in the irradiated group. VEGF and CD31 expression was increased in irradiated kidneys at both mRNA and protein levels(p<0.01). Exp3: One-way analysis of variance followed by Tukey’s test showed that, following I/R, Blood Urea Nitrogen(BUN) and SCr levels were lower in the irradiated group compared to controls:BUN: 106.1±33.6 vs. 352.2±54.3mg/dl; SCr: 0.3±0.13 vs. 1.4±0.2mg/dl, and in irradiated group compared to the irradiated-exposed group to Sunitinib(BUN: 106.1±33.6 vs. 408.4±54.8mg/dl; SCr: 0.3±0.12 vs. 1.5±0.4mg/dl, p<0.01).
Conclusions: Renal radiation induces the activation of angiogenesis in mice. Renal irradiation leads to RIP, with preserved renal function and attenuated inflammation post I/R. Exposure to the anti-angiogenic drug Sunitinib post-irradiation prevents the irradiation-induced RIP.
Funding: Government Support - Non-U.S.

PO0427
Inhibition of 12/15 Lipoxigenase (12/15 LOX) Improves Renal Recovery and Function Post Ischemia-Reperfusion in Male Spontaneous Hypertensive Rats (SHR)
Rivaz Mohamed, Paul O’Connor, Jennifer C. Sullivan, August University, Augusta, GA.
Background: Acute kidney injury (AKI) due to ischemia-reperfusion (IR) is a serious and frequent complication with high mortality rates. The mechanisms mediating renal IR injury leading to increased risk of later developing cardiovascular and renal diseases in either sex remain poorly understood, although elevated 12/15-LOX activity has been reported to contribute to the progression of numerous kidney diseases. The goal of the current study was to test the hypothesis that enhanced activation of 12/15-LOX leading to impaired recovery post-IR.
Methods: 13-week-old male and female SHR were subjected to sham or 30-minute warm ischemia (IR, n=6-group). Additional male SHR were randomized to receive vehicle or the specific 12:15-LOX inhibitor ML335 (30 mg/kg i.p.; n=5/group) 1 hr prior to sham/IR and every other day up to 7 days post-IR. Blood and urine were collected from all rats 24 hrs and 7 days after IR; kidneys were harvested 7 days post-IR for biochemical, histological, and Western blot analysis.
Results: IR increased plasma creatinine (Pcr) and blood urea nitrogen (BUN) in both male and female SHR compared to respective sham controls at 24 hrs (Pcr: p < 0.0001; P<0.01). At 7 days post-IR, Pcr and BUN remained elevated in male SHR but returned to pre-IR levels in females (Pcr: p < 0.03; P<0.04; BUN: p < 0.05; P<0.05). Histological examination of kidneys 7 days post-IR showed greater tubular damage (P<0.003; P<0.019) and renal cell death (P<0.01; P<0.01) in male vs. female SHR. Delayed recovery of renal function in male SHR was associated with increased renal 12/15-LOX (P<0.05; P<0.005) expression following IR. Post-IR treatment of male SHR with ML335 reduced IR-induced lipid peroxidation (P<0.01; P<0.0001) and increased levels of ER stress (P<0.05; P<0.05) compared to sham-controls. Pre-treatment of male SHR with ML335 reduced IR-induced lipid peroxidation (P<0.01; P<0.0001) and increased levels of ER stress (P<0.05; P<0.05) compared to vehicle-treated IR males 7 days post-IR.
Conclusions: In conclusion, our data demonstrate that enhanced activation of 12:15-LOX contributes to impaired renal recovery post-IR via ER stress and cell death in male SHR.
Funding: Other NIH Support - AHA and NHLBI, Private Foundation Support

PO0428
The Immunomodulatory Effect of LMWFA5 on Infiltrating Immune Cells Supports Its Clinical Use for AKI
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Background: Infiltrating immune cells are critical to acute kidney injury (AKI) pathogenesis. They are activated to clear cellular debris, secrete pro-inflammatory mediators, and activate leukocytes, which can lead to production of anti-inflammatory mediators that promote tissue repair. However, dysregulated, continuous, or excessive immune activation can result in further tissue damage. The <5kd low molecular weight fraction of human serum albumin (LMWFA5) has anti-inflammatory/ immunomodulatory effects. This shows urgently needed to evaluate the ability of LMWFA5 to treat AKI by examining its effects on immune cells relevant to AKI.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Peripheral blood mononuclear cells (PBMC) were treated with vehicle control or LMWF5A and activated with lipopolysaccharide (LPS), LPS + interferon (IFN) γ, or interleukin (IL)-4 + IL-13. Media and total RNA were collected at 24h. Secreted molecules were analyzed using multiplex cytokine arrays or prostaglandin E2 (PGE2) ELISA, and differential gene expression was determined by mRNAseq. Data were then subjected to in silico interrogation of known AKI signaling pathways and comparison to public datasets featuring human AKI samples.

Results: Cytokine release by PBMC was significantly modulated by LMWF5A treatment. While cytokine profiles differed depending on stimulant, the most highly downregulated cytokines included C-X-C chemokine ligand 10, IFNγ, IL-10, IL-12, IL-17, monocyte chemotactic protein (MCP)-1, and MCP-3 (n=5; p<0.05), which have been implicated in AKI. In addition, the release of PGE2, which has been proven to be beneficial to kidney injury, was potentiated with LMWF5A treatment. In silico secretome and transcriptome analyses of LMWF5A-treated PBMC displayed predicted inhibition of pathways known to drive AKI, notably IFN and IL-17 signaling. Further, comparison to public human AKI biopsy data revealed that pathways activated by AKI were predicted to be significantly inhibited in LMWF5A-treated PBMC.

Conclusions: These data reflect the ability of LMWF5A to reduce inflammatory cytokines and shift the immune response towards resolution. Moreover, global regulation of pathways activated by AKI in kidney tissue are predicted to be inhibited by LMWF5A. This preliminary study suggests a potential role for LMWF5A as an effective AKI therapeutic.

Funding: Commercial Support - Ampio Pharmaceuticals

PO0429
Mutation of Regulatory Phosphorylation Sites in PFKFB2 Does Not Affect Metformin’s Protective Effects Against Renal Fibrosis

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Background: Metformin has been shown to have protective effects in mouse models of renal fibrosis via its effects on fatty acid oxidation but the contribution of glycolysis to this effect is unclear. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB) is a key regulator of glycolysis in the kidney and is not believed to have an effect on fatty acid oxidation. We aimed to determine if modification of glycolysis has a critical role in metformin’s protective effects against renal fibrosis.

Methods: Mice with inactivating mutations of the phosphorylation sites in PFKFB2 (PFKFB2 KI mice) were generated, which is predicted to reduce the ability to increase the rate of glycolysis following stimulation. These were compared with wild-type controls. Mice were administered metformin via drinking water and a unilateral ureteric obstruction (UUO) model was used. The degree of fibrosis was assessed by Western blot and RT-PCR.

Results: In the PFKFB2 KI mice treated with metformin, there was decreased fibrosis following UUO as assessed by Western blot for fibronectin (p<0.05) and RT-PCR for alpha-SMA, collagen-3 and F4.80. There was no significant difference between WT and PFKFB2 KI mice treated with metformin in regards to the degree of fibrosis following UUO in any of the Western blot or RT-PCR parameters that were measured.

Conclusions: These data show that inhibition of the regulation of glycolysis by PFKFB2 does not prevent metformin from having protective effects against renal fibrosis in a UUO model.

Funding: Government Support - Non-U.S.

PO0430
Scaffold Protein Na+/H+ Exchanger Regulatory Factor 1 (NHERF1) Protects Tenofovir-Induced Nephrotoxicity by Regulating Na+/Pi Cotransporter (Npt) and Intracellular Phosphorus Balance

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Background: Tenofovir disoproxil fumarate (TDF) could cause proximal tubular (PT) dysfunctions and eGFR decline with mitochondria damages. PDZK1, MAP17, and NHERF1 are scaffold proteins that influence the localization and function of membrane proteins. We tried to investigate the changes of both membrane-associated proteins and proximal tubular transporters in TDF-induced nephrotoxic model.

Methods: C57BL6 mice (n = 8) were gavaged daily with 10mg/kg/d, 50mg/kg/d of TDF for 8 weeks. The human renal tubular epithelial cells (HK-2) were grown and received 24 to 72 h exposure to 0–128 µM TDF or vehicle. NHERF1 was overexpressed in HK-2.

Results: Chronic TDF administration to mice resulted in swollen and exfoliated tubular epithelial cells, brush border cilia lodging and dissolving, and serum creatinine elevation (P<0.05, mean 10.23±2.683 vs. 27.18±18.41) compared to the control group. The protein expressions of scaffold protein NHERF1, Na+-Pi cotransporter (Npt), and sodium-glucose cotransporter type 2 (SGLT2-2), but not PDZK1 and MAP17 were decreased in the kidneys of TDF-treated mice and cells. The intracellular phosphorus concentrations decreased dose-dependent with TDF concentration and the exposing time, compared with down-regulated Npt expressions. ATP levels reflected mitochondrial functions were also decreased with a time and dose-dependent exposure of TDF. NHERF1 overexpressing cells are well resistant to transporter damage and mitochondrial damage caused by TDF.

Conclusions: NHERF1 protects the TDF-induced AKI by Npt, intracellular phosphorus, and mitochondria dysfunction pathway.

Figure 1. Representative light micrographs and electron micrographs of mice kidney.

PO0431
Renal Papillary Function and Repair After Reversible Ureteral Obstruction

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Background: Models of reversible UUO (R-UUO) have provided insight into the mechanisms of repair in the renal cortex, but little is known about the mechanisms or extent of renal papillary repair after reversal of obstruction. Here we characterize long-term functional and structural papillary repair in a new mouse model of R-UUO.

Methods: Vascular clamps are placed on the L ureter, removed on day 7, and a R nephrectomy (Nx) performed on day 17. We evaluated serial BUN; transdermal GFR (gGFR); urinary osmolarity (OSM) after water restriction; histology and fibrosis; tubules, and capillaries; and urine albumin, AQP1 and 2 were restored by day 84, but there was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was a reduction in capillary density by CD31 staining days 14>84. Lineage analysis with Six2-CRE; R26R-td Tomato reporter mice to assess repair of nephronic epithelium.

Results: At clamp removal (day 0) all mice had hydronephrosis. 60-80% survived 48hrs after Nx, and day 14 BUN in Nx vs. R-UUO+Nx was 18.5 (0.9) vs. 42.6 (8.5) ng/dl, p<0.001, indicating reversal and consistent injury. gGFR was reduced at day 28 (991.0 (46.6) vs. 569.8 (82.6) ml/min/100gm, p<0.001), reversed by day 84, with decreased urinary OSM up to day 84 (3525 (106.9) vs. 1718 (175.7) mmol/L, p<0.0001). There was cortical fibrosis from 0-84 days. Fibrosis increased day 0-28 in the papilla but was absent by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was loss of AQP1 (descending thin limb, DTL) and AQP2 but not LTL staining. Total collecting duct, (CD) days 3-28. AQP1 and 2 were restored by day 84, but there was a reduction in capillary density by CD31 staining days 14-84. Lineage analysis showed persistent Six2 lineage in the papilla at day 28, indicating effective repair of nephronic epithelium.

Conclusions: At clamp removal (day 0) all mice had hydronephrosis. 60-80% survived 48hrs after Nx, and day 14 BUN in Nx vs. R-UUO+Nx was 18.5 (0.9) vs. 42.6 (8.5) ng/dl, p<0.001, indicating reversal and consistent injury. gGFR was reduced at day 28 (991.0 (46.6) vs. 569.8 (82.6) ml/min/100gm, p<0.001), reversed by day 84, with decreased urinary OSM up to day 84 (3525 (106.9) vs. 1718 (175.7) mmol/L, p<0.0001). There was cortical fibrosis from 0-84 days. Fibrosis increased day 0-28 in the papilla but was absent by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was loss of AQP1 (descending thin limb, DTL) and AQP2 but not LTL staining. Total collecting duct, (CD) days 3-28. AQP1 and 2 were restored by day 84, but there was a reduction in capillary density by CD31 staining days 14-84. Lineage analysis showed persistent Six2 lineage in the papilla at day 28, indicating effective repair of AQP1- DTL. There was a marked increase in Kir7+ Six2 lineage and LTL+ CD cells days 3-7 after reversal, but no expression of the de-differentiation marker, Sox8, in the papilla.

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PO0432

The Susceptibility Mechanism of AKI in Cirrhosis Through Regulation of miR-599 Mediated by SIRT1

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Background: Previous study has confirmed that SIRT1/PGC-1α signaling pathway might be involved in the pathogenesis of acute kidney injury (AKI) in cirrhosis. This study aimed to analyze the association between SIRT1 single nucleotide polymorphism (SNP) and the risk of AKI in cirrhosis.

Methods: A total of 29 patients in AKI group and 87 patients in control group were selected from a Chinese Han population. Genotypes of SIRT1 rs4746720 and rs2273773 were detected by SnaPshot technology. Bioinformatics softwares predicted that miR-599 might bind to the rs4746720 locus within SIRT1 3’UTR. The dual luciferase reporter vectors pmirGLO-SIRT1-3’UTR-T/C were constructed and respectively co-transfected with miR-599 mimic or NC into HK-2 cells. The overexpression recombinant plasmids pcDNA3.1-SIRT1-T/C were further constructed and respectively co-transfected with miR-599 mimic, miR-599 inhibitor or NC into HK-2 cells, and the expression of miR-599 and SIRT1 was measured by qRT-PCR and Western blot.

Results: There was no significant association between SIRT1 SNP and the risk of AKI in cirrhosis (P>0.05). But stratified analysis based on risk factors showed that in the subgroup of hepatic encephalopathy, SIRT1 rs4746720 polymorphism was significantly associated with the risk of AKI in cirrhosis (OR=6.08, 95%CI 1.22-29.48, P=0.027). Analysis of liver and kidney function showed that Scr and BUN of TT genotype of subgroup of hepatic encephalopathy, rs4746720 polymorphism was significantly higher than that of CC+CT genotype (P<0.05). Neither SIRT1/PGC-1α/TFLLR-NH2-augmented increased SCr levels induced by dabigatran in a dose-dependent manner in the 5/6NE. Interestingly, both PAR1 activation peptide and PAR1 inhibition with the PAR-1 inhibitor SCH79797 (0.25 mcmol/kg/day) significantly decreased the SCr levels induced by dabigatran. The reduction of SNP and the risk of AKI might be involved in the pathogenesis of acute kidney injury (AKI) in cirrhosis.

Conclusions: The reduced SNPs of SIRT1 3’UTR may be associated with the risk of AKI in patients with cirrhosis. The rs4746720 T allele of SIRT1 may mediate the binding of miR-599, affect the expression of SIRT1 and its downstream pathway.

PO0433

RAP Inhibits Proximal Tubule Endocytosis and Protects Against Gentamicin-Induced Nephrotoxicity

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Background: The proximal tubule (PT) reabsorbs and concentrates filtered nephrotoxins by clathrin mediated (CME) and fluid phase mediated (FPE) endocytosis, leading to PT injury and AKI. The molecular chaperone RAP (Alpha-2-macroglobulin receptor-associated protein) a 39kDa protein inhibits LDL receptor family members lipoprotein binding, including megalin. Our hypothesis was that RAP would inhibit megalin mediated CME, but not FPE, and reduce gentamicin nephrotoxicity.

Methods: We utilized daily injections of gentamicin (100mg/Kg, IP) in a nephrotoxic dose scheme. GPNMB mRNA was expressed at low levels in the kidneys of normal mice or rats, a robust induction of GPNMB mRNA was observed following kidney ischemia reperfusion injury (IRI). Here we investigated the role of GPNMB mRNA in the regulation of glomerular filtration barrier integrity in 5/6NE. Male SD rats were subjected to 40 min of bilateral renal ischemia. Kidneys were harvested on day 5 and day 6. MCSF- primed human M1 or M2 macrophages were isolated from human LeukoPaks. In human proximal epithelial HK2 and RPTEC cells, an AMPK activator was used to induce GPNMB expression. GPNMB is an AMP-activated protein kinase (AMPK) upregulated gene in whole bloods. GPNMB deficient mice fail to undergo repair and injury resolution following kidney ischemia reperfusion injury (IRI). Here we investigated the role of GPNMB expression in the rat IRI and mouse cisplatin AKI models with or without an AMPK activator treatment. We also characterized GPNMB expression in human proximal epithelial cells, M1 and M2 macrophages.

Results: RAP injections markedly reduced S1 PT albumin uptake over minutes (80%). Experiments were performed in normal rats in a rapid and fully reversible fashion. In rats treated with or without RAP, daily gentamicin treatment resulted in elevated serum Cr by day 5 (1.4 ± 0.2 vs. 3.1 ± 0.4mg/dl, p<0.001) and day 6 (1.5 ± 0.5 vs 5.4 ± 0.8mg/dl, p<0.001). Ccr decreased on day 6 to 0.49 ± 0.16 ml/min vs 0.09 ± 0.07 ml/min and urinary protein increased to 488 mg/mil/100mg wt vs 2,512 mg/mil/100 gm wt in RAP treated and untreated rats, respectively.

Conclusions: These results indicate RAP treatment induced reductions of both CME and FPE PT endocytosis suggesting a link between megalin and FPE. Clinically, RAP may have direct relevance to preventing the harmful nephrotoxic effects of gentamicin treatment, and likely other nephrotoxins, especially in individuals more susceptible to aminoglycoside injury. Future studies will need to explore whether reductions in ototoxicity are also prevented.

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PO0434

Role of Protease-Activated Receptor 1 (PAR1) in Glomerular Filtration Barrier Integrity

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Background: Protease-activated receptors (PARs) play a significant role in the regulation of angiogenesis and fibrosis. Their role in the regulation of glomerular filtration barrier (GFB) function is incompletely elucidated. We had demonstrated that PAR1 inhibition with SCH79797 results in glomerular hemorrhage and acute kidney injury in the 5/6 nephrectomy rats (5/6NE), effects similar to those of a direct thrombin inhibitor (dabigatran) and mimic features of anticoagulant-related nephropathy in humans. The aim of the current study was to investigate potential synergistic effects of dabigatran with PAR1 inhibition or agonism in 5/6NE.

Methods: Three weeks after surgery 5/6NE rats were treated with dabigatran (150 mg/kg/day) alone or with PAR-1 inhibitor SCH79797 (1.0 mg/kg/day and 3.0 mg/kg/day) or PAR1 activation peptide, TFLL-R-NH2 10.25 mcmol/kg/day and 0.5 mcmol/kg/day. Serum creatinine (SCr), activated partial thromboplastin time (aPTT), and hematuria were measured daily; kidney morphology was evaluated at the end of the study.

Results: As expected, treatment with PAR1 modulators did not alter the anticoagulant effects of dabigatran and did not prolong aPTT when used alone. Both SCH79797 and TFLL-R-NH2 aggregated increased SCr levels induced by dabigatran in a dose-dependent manner in the 5/6NE. Interestingly, both PAR1 activation peptide and PAR1 inhibition with SCH79797 significantly decreased the SCr levels induced by dabigatran. The reduction of SNP and the risk of AKI might be involved in the pathogenesis of acute kidney injury (AKI) in cirrhosis.

Conclusions: PAR1 homodimers are necessary to maintain GFB integrity in 5/6NE. Pharmacological activation or inhibition of PAR1 results in glomerular hematuria and acute kidney injury in 5/6NE. These effects are similar to those of dabigatran-mediated thrombin inhibition in 5/6NE, suggesting that the thrombin-PAR1 signaling axis is important to GFB function.

Funding: NIDDK Support

PO0435

Renal GPNMB is Highly Upregulated in Rodent Models of AKI and is Further Elevated with Pharmacological AMPK Activation


Background: Glycoprotein nonmetastatic melanoma B (GPNMB) is highly expressed in macrophages. GPNMB is an AMP-activated protein kinase (AMPK) upregulated gene in whole bloods. GPNMB deficient mice fail to undergo repair and injury resolution following kidney ischemia reperfusion injury (IRI). Here we investigated the role of GPNMB expression in the rat IRI and mouse cisplatin AKI models with or without an AMPK activator treatment. We also characterized GPNMB expression in human proximal epithelial cells, M1 and M2 macrophages.

Methods: RPTEC and HK2 cells were exposed to hypoxia for 24 h. GMCSF- or MCSF- primed human M1 or M2 macrophages were isolated from human LeukoPaks. Male SD rats were subjected to 40 min of bilateral renal ischemia. Kidneys were harvested 2 days after IRI. Male C57B mice were administered with a single injection of cisplatin. Kidneys were harvested 72 h after cisplatin injection.

Results: In human proximal epithelial HK2 and RPTEC cells, an AMPK activator treatment resulted in a dose-dependent increase of GPNMB mRNA. Significant increase of GPNMB mRNA was observed in HK2 and RPTEC cells cultured in hypoxic versus normoxic conditions. We also demonstrated that AMPK activation increased IFNy and LPS-induced GPNMB secretion in human M2 but not M1 macrophages. After a single oral administration of an AMPK activator in normal mice or rats, a robust induction of GPNMB mRNA in the whole blood was seen starting 3 h and lasting up to 22 h. We found that GPNMB mRNA was expressed at low levels in the kidneys of normal mice or rats. GPNMB mRNA was markedly up-regulated following IRI in the kidneys at 48 h.

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176
In a mouse cisplatin-induced AKI model, a dramatic increase of GPMB mRNA was observed in the kidneys. Phase-microarray activation of AMPK in both AKI models resulted in further increase of renal GPMB.

**Conclusions:** GPMB mRNA is highly up-regulated in the kidneys of rat IRI and mouse cisplatin AKI models and is further elevated after an AMPK activator treatment. GPMB can serve as a marker for AMPK activation in tubular epithelial cells, M2 macrophages, and whole bloods. Our results support that GPMB could modulate macropages polarization which may be involved in inflammation and immune response, contributing to injury and repair post AKI.

**Funding:** Commercial Support - Janssen Pharmaceutical Research & Development of Johnson & Johnson

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**PO0436**

**Loss of Stimulator of Interferon Genes (STING) Pathway Does Not Prevent the Kidney Against Acute Injury or Inflammatory and Fibrotic Pathways Induced by Folic Acid**

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**Background:** Acute kidney injury (AKI) greatly increases the risk for developing chronic kidney disease (CKD), but it is currently not well understood how this progression from injury to inflammation and fibrosis takes place. Recently it was discovered that with injury, damaged mitochondria in the kidney can leak mitochondrial DNA into the cytosol, where it activates the cyclic GMP-AMP synthase (cGAS) stimulator of interferon genes (STING) pathway causing inflammation and fibrosis. To explore the significance of this pathway in the setting of AKI and CKD transition we induced folic acid nephropathy in mice with no detectable STING activity and evaluated them for kidney function and inflammation/fibrosis by quantification of potassium 7 days after administration.

**Methods:** 23-week Goldenticket (GT) mice (no detectable STING protein due to a missense mutation) and age matched wild type (WT) littermate controls were injected with 250 mg/kg of folic acid. Seven days later plasma, urine, and kidneys were collected for analysis of plasma creatinine, blood urea nitrogen (BUN) and urinary albumin. Renal creatinine ratio (uACR). 8 mice were used for both WT and GT vehicle groups and 11 mice were used for WT and GT groups treated with folic acid.

**Results:** In WT control mice folic acid treatment significantly elevated plasma creatinine from 0.27±0.06 to 0.62±0.33mg/dl, BUN levels from 25±1.3 to 66.8±2.1mg/dl, and uACR more than doubled from 21.3±1.4 to 53.5±6.4mg/mg. This effect was not statistically different from what was observed in GT mice (plasma creatinine increasing from 0.25±0.04 to 0.55±0.20mg/dl, BUN increasing from 20.9±1.9 to 54.7±2.1mg/dl, and uACR increasing from 15.9±1.8 to 140.2±313.5mg/mg with folic acid, respectively). Kidney gene expression for genes involved in fibrosis (Tgf-β, Col1a1) inflammation (Tnf, Il6, Il1b), and apoptosis (Bax, Trp53) were all elevated with folic acid treatment. Only Il6 which is a direct effector gene of STING, was significantly decreased in the folic acid treated GT mice as compared to the folic acid treated WT controls.

**Conclusions:** Ablation of STING did not protect kidney function, nor did it impart fibrogenic or inflammatory gene expression. Our data suggest that the cGAS/STING pathway is not involved in the development of AKI and in the transition to CKD in the folic acid nephropathy model.

**Funding:** Commercial Support - Janssen Research & Development LLC

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**PO0437**

**Extracellular Matrix Protein 1 Organized Microenvironment Keys to Kidney Repair After AKI**

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**Background:** In AKI, the kidney tubule is well-known as the epicenter of damages, yet little attention has been paid to changes in the microenvironment and associated repair processes. Amid this process, the extracellular matrix (ECM) is the principal organizing component for microenvironment construction and tubule repair, serving as a scaffold for remodeling. How ECM interacts with its surrounding materials to dictate the prognosis of AKI remains unclear in the field.

**Methods:** Kidney ischemia-reperfusion injury was employed to induce AKI in mice. *In vivo, in vitro*, and *ex vivo* translational experiments and quantitative proteomic analyses were performed.

**Results:** Quantitative proteomics revealed that extracellular matrix protein 1 (ECM-1) was the earliest activated matrix protein in ischemic AKI kidneys. Immunostaining revealed that ECM-1 was predominantly expressed in the activated kidney fibroblasts. In cultured fibroblasts, knockdown ECM1 markedly repressed cell activation and proliferation, as assessed by the decreased expression of α-SMA, vimentin, PDGFR-β, and PCNA. *Ex vivo*, knockdown ECM1 in the decellularized AKI kidney scaffold directly reduced its capacities in promoting the proliferation of the seeded tubular cells. *In vivo*, loss of ECM1 caused elevated serum creatinine levels, more severe morphologic changes, and reduced inductions of α-SMA, vimentin, and PDGFR-β than the controls after AKI. By using affinity-purification mass spectrometry, we identified a vital mechanism that ECM1 could bind to an essential tubule-derived growth factor protecting against AKI, sonic hedgehog (Shh). In *in vivo*, we confirmed that recombination ECM1 promoted tubular cell proliferation and Shh expression.

**Conclusions:** Our finding implicated that ECM1 created a favorable microenvironment by interacting with Shh to promote AKI recovery.

**Funding:** NIDDK Support

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**PO0438**

**TNF Drives AKI-to-CKD Transition Downstream of Proximal Tubule EGFR**

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**Background:** Inflammation is a key driver of fibrosis and progression of human chronic kidney disease (CKD), often caused or worsened by acute kidney injury (AKI-to-CKD transition). Sustained epithelial-growth-factor-receptor (EGFR) activation in injured proximal-tubule-cells (PTC) is strongly pro-inflammatory and has emerged as a key paradigm in AKI-to-CKD transition and CKD progression. Whether the key type 1 inflammatory cytokine tumor-necrosis-factor (TNF) has a role in CKD progression and how TNF relates to the PTC in AKI and CKD pathology is unclear.

**Methods:** We compared mice treated with control, TNF-inhibition (etanercept, TNF-scavenger), EGFR-inhibition (erlotinib, EGFR-kinase-inhibitor) or their combination in an AKI-to-CKD bilateral renal-ischemia-reperfusion model.

**Results:** TNF- or EGFR-inhibition did not affect initial kidney injury, but significantly suppressed in reducing kidney injury-upregulated cytokines and equally strongly reduced kidney fibrosis, while combination treatment had no additive effect, suggesting EGFR and TNF act in the same fibrosis pathway. TNF exerted its profibrotic effects downstream of PTC-EGFR, as TNF-inhibition did not affect tubular egfr activation in vivo. Consistent with this, TNF-PTC-KO did not reduce inflammation or fibrosis, suggesting that PTC-derived TNF does not contribute to profibrotic PTC-EGFR activation. Kidney single-cell-RNAseq analysis identified macrophages, dendritic cells and T cells, but not PTC, as dominant TNF sources after AKI. Only EGFR-inhibition, but not TNF-inhibition significantly blocked injury-induced kidney ingress of macrophages, however, macrophage numbers where equal one month after AKI independent of treatment. Thus EGFR-inhibition reduces ingress and accumulation of TNF-producing proinflammatory and profibrotic immune cells whereas TNF-inhibition mechanistically largely acts by neutralizing their proinflammatory and profibrotic activities.

**Conclusions:** Our work provides mechanistic background to motivate examination of TNF pathway inhibition in human AKI or CKD.

**Funding:** NIDDK Support, Private Foundation Support

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**PO0439**

**Antioxidant Prevents Detrimental Heart-Kidney Cross-Talk in a Novel Experimental Model of Cardiorenal Syndrome due to Isolated Right Heart Failure**

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**Background:** Since recognition of CRS, most studies have investigated left heart failure and outcomes due to isolated RVF are under recognized. However, renal dysfunction is an independent predictor of death and hospitalization in RVF. To examine experimental models of CRS improve our understanding of the pathophysiology of RV-Kidney interaction and enable us to explore new therapeutic modalities.

**Methods:** In a alkali (ALK) injection induced CRS in rats we investigated whether antioxidant prevents deleterious interactions of RV-Kidney in CRS. Rats were treated with an antioxidant, 1 wk pre & post-ALK injection. At 3 and 4 wks post-ALK injection, serial echocardiography was performed to monitor cardiac function. RV systolic pressure (RVP), RV hypertrophy (Rvh), RV function, RV levels of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and lipid peroxidation (LPx) were measured. After sacrificing animals, hearts and kidneys were removed for histopathology.

**Results:** At 4 weeks, ALK-induced CRS resulted in increased mortality, RVP, RVh, and LPx in RV myocardium accompanied RVF as well as the kidney. Antioxidant enzymes activities including SOD and GSHPx were decreased in RV and the kidney. Kidney histopathology with Periodic acid-Schiff (PAS) staining demonstrated tubular epithelial denudation, a marker of ATN that was not seen at 3 weeks post-ALK injection. This excludes renal toxicity of the alkali. An antioxidant treatment prevents not only ALK induced CRS and decreased oxidative stress but also increased the SOD and GSHPx levels in the RV myocardium and the kidney.

**Conclusions:** A reduction in oxidative stress by antioxidant may explain the prevention of ALK-induced CRS. Thus, targeting oxidative stress may lead to the development of novel therapies for CRS and antioxidants as an adjuvant therapy may be beneficial.

**FPO440**

**Inability to Increase Fatty Acid Oxidation Worsens AKI and Impacts the Benefit of Metformin**

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**Background:** Energy metabolism is critical to the pathogenesis of ischemic acute kidney injury (AKI) - its role in nephrotoxic AKI is less understood. Fatty acid oxidation (FAO), the kidney’s most important energy source, is regulated by acetyl-CoA carboxylase (ACC) and is augmented during high fat feeding and during oral glucose administration of ACC. We aimed to determine whether regulation of FAO affects the outcome of nephrotoxic AKI.

**Methods:** Cisplatin AKI was induced in ACC knockin (KI) mice, which have mutations of ACC phospho-sites that disrupt FAO regulation, and compared to wild-type (WT) controls. A primary tubular epithelial cell (TTEC) culture model of cisplatin toxicity was used to further study the findings.

**Results:** Cisplatin AKI was induced in ACC knockin (KI) mice, which have mutations of ACC phospho-sites that disrupt FAO regulation, and compared to wild-type (WT) controls. A primary tubular epithelial cell (TTEC) culture model of cisplatin toxicity was used to further study the findings.
Results: ACC KI mice demonstrated more severe cisplatin-AKI versus WT as assessed by day 2 serum urea (ACC KI 40.5±11.6 mM vs WT 27.2±7.6 mM, p < 0.005) and creatinine (ACC KI 0.09±0.03 mM vs WT 0.06±0.03 mM, p < 0.05). Western blot for neutrophil gelatinsase associated lipocalin (NGAL) was increased 9.3±2.1 fold in ACC KI compared to 3.3±3.4 fold in WT (p=0.0001 for ACC KI vs WT). WT and ACC KI TEC cultures exposed to cisplatin revealed increased apoptosis in ACC KI, as assessed by increased cleaved caspase-3 (cCasp3) (p<0.0001). In TECs, metformin was protective against cisplatin mediated apoptosis, however this was diminished in ACC KI cells (cCasp3 reduced 49.5%) versus WT cells (cCasp3 reduced 72%) (p=0.03 for ACC KI vs WT).

Conclusions: Severity of nephrotoxic AKI is dependent on maintaining regulation of FAO. Metformin reduces cisplatin-AKI severity by its ability to increase FAO.

Funding: Government Support - Non-U.S.

PO0441
Caloric Restriction Reduces the Pro-Inflammatory Eicosanoid 20-HETE to Protect from AKI
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Background: Acute kidney injury (AKI) is a frequent complication in the clinical setting and associated with significant morbidity and mortality. Preconditioning with short-term caloric restriction (CR) is highly protective against kidney injury in rodent ischemia-reperfusion-injury (IRI) models, but the underlying mechanisms are unknown hampering clinical translation. The aim of this work was to further characterize possible mechanisms of protective effects of preconditioning.

Methods: 14-week-old male and female C57Bl6 wild-type mice underwent no short-term caloric restriction (CR) is highly protective against kidney injury in rodent ischemia-reperfusion-injury (IRI) models, but the underlying mechanisms are unknown hampering clinical translation. The aim of this work was to further characterize possible mechanisms of protective effects of preconditioning.

PO0442
The MLL1/WDR5 Complex Contributes to Cisplatin-Induced Renal Epithelial Death by Promoting p53-mediated E-Cadherin Repression Chunyun Zhang,1 Yingjie A. Guan,1 George P. Bayliss,2 Shougang Zhuang,1,2 1Rhode Island Hospital, Providence, RI; 2Shanghai East Hospital, Shanghai, China.

Background: The mixed-lineage leukemia 1 (MLL1)/WD-40 repeat protein 5 (WDR5) complex is a methyltransferase deemed a positive regulator of histone H3 lysine 4 trimethylation (H3K4me2) and functions as an oncogenic factor in many cancer types. The role of the MLL1/WDR5 complex in acute kidney injury (AKI) and renal epithelial cell death is still unclear. In this study, we investigated the role and mechanism of this complex in the apoptosis of renal epithelial cells following cisplatin exposure.

Methods: Cultured kidney proximal tubular (TKPT) cells were exposed to cisplatin in the presence or absence of MM102, a MLL1/WDR5 protein–protein interaction inhibitor or small interfering RNAs (siRNA) specific targeting MLL1 or WDR5.

Results: Expression of MLL1, WDR5 and H3K4me3 as well as phospho-p53 and cleaved caspase 3 were increased whereas that of E-cadherin was decreased in cultured TKPT cells exposed to cisplatin in a time dependent manner. Inhibition of the MLL1/WDR5 complex with MM102 or siRNA-mediated silencing MLL1 or WDR5 attenuated cisplatin induced cleavage of caspase 3 and cell death, which was coincident with downregulation of p-p53 and preservation of E-cadherin expression. Inhibition of p53 by pifithrin-α also alleviated cisplatin-induced cell death and restored E-cadherin expression in TKPT cells with or without MM102 treatment. In contrast, activation of p53 by Nutlin prevented TKPT cell death and E-cadherin repression. Moreover, siRNA mediated silencing of E-cadherin attenuated the protective effect of MM102 following cisplatin treatment while expression of p-p53 was not affected. Finally, we found that pharmacological inhibition of MLL1/WDR5 reduced cisplatin-induced phosphorylation of ataxia-telangctasia mutated protein, ataxia telangctasia and Rad3-related protein, checkpoint kinase 1 (Chk1), checkpoint kinase 2 (Chk2) and γ-H2AX, which are activated in response to DNA damage and associated with p53 transcriptional activation.

Conclusions: These data suggest that the MLL1/WDR5 complex may contribute to cisplatin-induced apoptosis of renal tubular epithelial cells by promoting p53-mediated E-cadherin repression following DNA damage. Targeting the MLL1/WDR5 complex may have a therapeutic potential for the treatment of cisplatin-induced AKI.

Funding: NIDDK Support

PO0443
Comparison of Inflammatory Responses in Sepsis-Induced AKI Mouse Models and Response to Dexamethasone
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Background: AKI occurs in the majority of patients with severe sepsis and contributes to high morbidity and mortality. Despite the frequency of AKI, the underlying mechanisms of renal injury during sepsis are not fully understood, and approved therapies to prevent or reverse this condition. Systemic and local inflammatory responses play a large role in the development of sepsis induced acute kidney injury (S-AKI).

Methods: To develop novel treatments for patients with S-AKI, animal models of polymicrobial sepsis are used; the most widely reported models being cecal ligation puncture (CLP) and cecal slurry (CS). We compared the acute (24h) renal function and inflammatory response of these two models, as well as the ability of dexamethasone (dexa) to prevent the development of S-AKI.

Results: CLP significantly reduced renal function, with increased plasma creatinine (0.18±0.11 mg/dL), blood urea nitrogen (BUN, 81.11±128.8 mg/dL), and increased inflammatory markers IL-6 (127±73 ng/mL), TNF-α (176±33 pg/mL), and IL-1β (164±141 pg/mL) compared to sham animals. Dexa (8 mg/kg) significantly decreased plasma creatinine (0.11±0.01 mg/dL), BUN (103±20 mg/dL), cystatin C (2443±134 pg/mL), IL-6 (124±63 ng/mL), TNF-α (134±39 pg/mL) compared to basal levels. Dexa treatment (2.5 mg/kg) significantly decreased creatinine, cystatin C, IL-6, TNF-α, and IL-1β. In this study, we have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexa. Our results suggest that the CS model may be provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.

Conclusions: We have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexa. Our results suggest that the CS model may be provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.
Prohibitin Ligand FL3 Protects Renal Proximal Tubular Cells Against ATP-Depletion-Induced Injury
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Background: FL3 is a synthesized ligand of prohibitins, a family of proteins located on and important for mitochondrial inner membrane. FL3 has been reported to protect neurons and cardiomyocytes by regulating mitochondrial function. Whether FL3 can protect kidney cells against cell stress remains unknown. This study aims to evaluate the effect of FL3 on ATP-depletion-induced cell death in renal proximal tubular cells (RPTCs).

Methods: RPTCs were pre-treated with 50 nM FL3 for 3 hours and incubated with 10 mM azide in glucose-free Krebs-Ringer bicarbonate solution for 3 hours to induce ATP depletion. The cells were then returned to a normal culture medium for recovery. Cells were also exposed to the same concentration of FL3 throughout the ATP depletion and recovery phases. The basal changes including mitochrondrial fragmentation, Bax translocation, cytochrome C release, prohibitin complex breakdown, OMA1, and OMA1 proteolysis were examined immediately after azide treatment; whereas apoptosis events including apoptosis and caspase activation were examined after 2 hours of recovery.

Results: RPTCs with azide-induced ATP depletion developed apoptosis morphology, caspase 3 activation and PARP cleavage, which were suppressed by FL3. Mitochondrial fragmentation and membrane leakage of cytochrome C were increased in RPTCs during ATP depletion. FL3 suppressed mitochondrial fragmentation and inhibited mitochondrial injury. Under cell stress, the large prohibitin ring complex was disrupted to medium and small complexes, releasing OMA1 to cleave the inner membrane protein OMA1. FL3 treatment decreased both the small prohibitin complex and the activation of OMA1. FL3 also partially prevented the degradation of the long isoforms of OPA1 during ATP depletion.

Conclusions: FL3 can protect against ATP-depletion-induced injury in renal tubular cells, likely through the regulation of mitochondrial dynamics.

Funding: NIDDK Support, Veterans Affairs Support

Mechanisms of Aristolochic Acid I (AAI)-Induced Proximal Tubule Cell Injury
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Background: Aristolochic acids (AAs) are naturally occurring polyaromatic nitrogen compounds extracted from certain plants that were used to treat various diseases for centuries until their nephrotoxicity and carcinogenicity began to be recognized. Aristolochic acid I (AAI) is potentially one of the main pathogenic compounds and has been demonstrated to have nephrotoxic, carcinogenic, and mutagenic effects. Previous studies have indicated that AAI acts mainly on proximal renal tubular epithelial cells; however, investigation into the mechanisms of AAI-induced proximal tubule cell damage is still warranted.

Methods: Human kidney proximal tubule cells (PTCs; HK2 cell line) were exposed to AAI at different time points and concentrations in vitro. Cell proliferation, ROS generation, NO production, m-RNA/protein expressions and mitochondrial dysfunction was checked in HK2 cells after treatment with AAI.

Results: We found that AAI treatment decreased HK2 cell proliferation significantly at 24hrs with 40 μM concentration. AAI exposure increased ROS generation and decreased NO production. The protein expression studies demonstrated activation of innate immunity (TLRs 2, 3, 4 and 9, HMBG1), inflammatory (TNFA, IL6, IL18 and TGBF) and kidney injury (LCN2, KIM1) markers. In addition, our results indicated AAI-induced epithelial-mesenchymal transition (EMT) as well as mitochondrial dysfunction in HK2 cells.

Conclusions: AAI treatment caused injury to proximal tubule cells (HK2) through ROS-HMG1β/mtDNA mediated TLRs activation and inflammatory response.

AMPK Activation Alleviates TNF-α Induced Human Umbilical Vein Endothelial Cell Monolayer Permeability Increase

Background: The abnorol structural function and the renal microvasculature contributes to acute kidney injury (AKI) pathophysiology by reducing regional blood flow especially in the outer medulla. AKI results in marked increases in local and systemic cytokines, TNF-α, IL-1β, IL-6, and TNF-α orchestrate various inflammatory reactions increasing endothelial permeability due to loss of endothelial monolayer and alteration of endothelial cell-cell junctions. AMP-activated protein kinase (AMPK) has been reported to play a protective role in vascular function, mainly through eNOS phosphorylation, inhibition of ROS formation and stimulating mitochondrial biogenesis. In addition, AMPK has been reported to regulate the assembly and disassembly of epithelial tight junction. Objectives: Our aims were to investigate whether a direct small molecule AMPK activator could preserve endothelial cell monolayer integrity when challenged by TNF-α treatment, and to investigate the potential sites of AMPK-activation.

Methods: Structural and functional integrity of human umbilical vascular endothelial cells (HUVEC) attached monolayer was evaluated, and monolayer permeability by 2.5-5.5 μm increase was measured to reflect apoptotic cell death. TNF-α was used to induce injury. AMPK activation was confirmed by measurement of α-PAMP. Data were analyzed using 1-way ANOVA.

Results: 1, 10, 30, and 100 ng/ml TNF-α significantly induced HUVEC monolayer permeability after 24 hr treatment, with 11.2-, 8.1-, and 8.1-fold increases, respectively. Direct allosteric AMPK activator (CpdA) protected against permeability induced by 24 hr of 100 ng/ml TNF-α treatment, with a maximum reduction of 57.6% permeability at 100 μM CpdA (n=33,580, p<0.001). The cells treated with 100 ng/ml TNF-α for 24 hr were subjected to 2.8-fold CpdA treatment significantly protected cells from apoptosis in a dose dependent manner. TNF-α treatment for 6 hr increased HUVEC permeability (~6.4-fold), which was reduced (40.6% reduction) by CpdA treatment. Cells incubated with CpdA maintained their shape and cell-cell contacts and showed less intercellular gaps when compared to those treated with DMSO vehicle control.

Conclusions: AMPK activation alleviated endothelial leakage, potentially via decreasing apoptosis and maintaining cell-cell contacts. Our data supports AMPK activation as a novel therapeutic approach for AKI.

Funding: Commercial Support - Johnson & Johnson

SGLT-2 Inhibitor Dapagliflozin Does Not Improve Severe Ischemia-Reperfusion-Injured AKI
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Background: Acute kidney injury (AKI) is defined by a rapid decline in the kidney function, occurs in approximately 5-20% hospitalized patients and is associated with high mortality. Renal ischemia-reperfusion (IR) injury is a leading cause of AKI. Despite intensive research and progress in understanding the pathophysiological mechanisms, IR-AKI remains a critical problem in AKI. Furthermore without any effective treatment available, Dapagliflozin is a novel antidiabetic drug from the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors that reduce glucose reabsorption in renal proximal tubules. SGLT2 inhibitors have been recently suggested to cause protection even in a renal injury condition beyond diabetes, such as AKI. In our work, we aimed to test the effectiveness of dapagliflozin in decreasing kidney injury in a mouse model of severe IR-AKI.

Methods: We developed a mouse model of severe IR-AKI. C57BL/6j males underwent 35 minutes of renal ischemia by bilateral clamping of renal pedicles followed by 24 hr reperfusion. The levels of serum and urinary creatinine calculated 24 hr after reperfusion were high but all mice undergoing IR surgery survived. Histological analysis showed severe tubular injury in the outer stripe of outer medulla. Mice undergoing IR surgery were divided into groups and received either no treatment, 1 mg/kg dapagliflozin, 10 mg/kg dapagliflozin or vehicle only administered by oral gavage 24 hr and 1 hr before the onset of ischemia. BUN and other parameters of kidney function were assessed 24 hr after reperfusion.

Results: In our preliminary data oral administration of dapagliflozin did not prevent kidney function decline in the model of severe IR-AKI. The BUN levels in plasma at 24 hr after reperfusion were not significantly different in groups of mice undergoing IR surgery. This is in contrast to previously published study2 where, however, less severe model of IR-AKI with 27 minutes of renal ischemia was used.

Conclusions: Dapagliflozin did not improve severe IR-AKI. We hypothesize that dapagliflozin may be effective in improving less severe kidney injury, however, lacks effectiveness in more severe cases of AKI. In our future studies, we would like to test the ability of dapagliflozin to prevent kidney injury at different stages of IR-AKI. Chag et al. PLoS One. 2016;11(7):e0161250.

Funding: Other U.S. Government Support

Establishment and Evaluation of a Primary Human Renal Tubular 3D Spheroid Model for AKI and CKD
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Background: The proximal tubule of the nephron is a prime site for tubular injury due to its high energy requirements and its dependence on oxidative metabolism to meet its energy needs. Our understanding of the central role of mitochondrial abnormalities and alterations in metabolism in both acute and chronic kidney injury has steadily improved with potential targets to improve mitochondrial dysfunction that occurs in AKI and in AKI to CKD transition. Two-dimensional (2D) monolayer cultures and rodent animal models are unable to fully recapitulate clinical drug response, hence 3D models are being developed to provide a physiologically relevant context for the perm. and cortex. In brief,

Methods: Here, we developed a primary human renal tubular 3D spheroid culture model and established a cisplatin-injury model for therapeutic target evaluation. Human primary renal tubular cells (RPTEC) seeded in ULA plates showed aggregation after 4 hours and formed initial spheroids after 4 days and the primary cells can be cultured over 5 weeks without major physiological changes.

Results: In 3D setting, gene expression of tubular markers was significantly induced/restored close to the human tissue level compared to 2D culture (AQ1, OAT, LR2, PEP2, SLC12A1, etc.) suggesting a more physiologically relevant condition. As NAD+ levels decreased with protein to cell ratio, NAD+/NADH level dropped significantly.

Funding: Other U.S. Government Support

AKI: Novel Insights Poster

PO0444

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0449

Succinylation of Metabolic Enzymes Protects Against AKI
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Background: Acute Kidney Injury (AKI) is an increasingly prevalent outcome of hospitalizations, affecting up to 50% of ICU patients in America. Kidney function depends on the metabolic activity of Renal Proximal Tubule Epithelial Cells (RPTECs). To understand AKI pathology, we focused on a class of proteins that affect posttranslational modifications of major proteins, and especially the deacetylase Sirtuin 5 which is highly expressed in RPTECs. Our previous studies indicate that knockdown of this protein has a protective role in RPTECs post AKI which presents the exciting possibility of clinical translation in preventing or ameliorating any long-term damage from AKI.

Methods: Through independent pathway analysis and mass spectrometry we attributed the major protective effect of Sirt5 knockout to be succinylation of key mitochondrial and peroxisomal proteins, leading to a metabolic shift from mitochondrial Fatty Acid Oxidation (FAO) to peroxisomal-dependent FAO. To test this hypothesis in a less invasive manner than genetic knockdown, we used the mitochondrial FAAO inhibitor Etoximox and the peroxisomal stimulator Benzofurazan. In both cases we found a significant reduction in the kidney injury marker NGAL after ischemia-like injury.

Results: We postulate that the switch to more peroxisomal-mediated fatty acid oxidation is protective in association with a decrease in the Reactive Oxygen Species. To promote this shift, we investigated the effects of supplementing the mouse diet with medium-chain fatty acids (10% dodecanedioic acid) pre or post ischemia-reperfusion-injury (IRI). Mass spectrometry of the succinylation signature of murine kidneys after diet treatment was similar to that of the Sirt5 KO mice, suggesting a functional phenocopy. We have hypothesized that the switch to more peroxisomal-mediated fatty acid oxidation is protective due to a decrease in the Reactive Oxygen Species. To promote this shift, we investigated the effects of supplementing the mouse diet with medium-chain fatty acids (10% dodecanedioic acid) pre or post ischemia-reperfusion-injury (IRI). Mass spectrometry of the succinylation signature of murine kidneys after diet treatment was similar to that of the Sirt5 KO mice, suggesting a functional phenocopy. We have preliminary evidence that there is less oxidative stress when the dodecanedioic acid diet was administered pre- or post-injury and there is less overall damage to the proximal tubule epithelia.

Conclusions: The data from these experiments suggest a simple but effective diet treatment could reduce the burden of AKI cases.

Funding: NIDDK Support

PO0450

Efficacy and Safety of Roxadustat in Patients with Anemia of Dialysis-Dependent CKD (DD-CKD) Treated Continuously for ≥2 Years
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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is in development in the US for chronic treatment of anemia of CKD. This pooled post hoc analysis explored outcomes in DD-CKD patients (pts) treated with roxadustat for ≥2 years (y).

Methods: Pts were randomized to open-label roxadustat (n=2391) or placebo (PBO; n=1886) for up to 4 y in 3 Phase 3 DD-CKD trials (OLYMPUS, ALPS, ANDES). Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy. Data were analyzed in pts treated for ≥2y, regardless of rescue therapy use. P values are exploratory. Adverse events (AEs) were assessed.

Results: Overall, 789 roxadustat and 392 PBO pts were treated for ≥2y; of these, 87% and 85% completed treatment. Baseline (BL) values for roxadustat vs PBO were generally balanced: mean age 55 vs 57y, mean hemoglobin (Hb) 9.8 vs 9.7 g/dL, 59% vs 78% of pts had hypertension, 56% vs 60% of pts had diabetes, mean eGFR 21 vs 24 mL/min/1.73 m2. Change from BL to wk 25–28 (±2.0 vs ±0.5 g/dL; P<0.001), with differences seen from wk 4, and proportion of pts with Hb ≥10 g/dL vs wk 28–52 was higher (95% vs 32%). Roxadustat maintained Hb ≥10 g/dL to wk 100 (Figure). Mean roxadustat weekly dose increased by 11% from wk 25–28 to wk 97–100. Rescue therapy need (22% vs 34%) pts, including red blood cell (RBC) transfusion (13% vs 18% pts), was less with roxadustat vs PBO; IV iron use was 9% for both. Serious AEs rates with roxadustat vs PBO were 20 vs 17 per 100 pt-exposure years, respectively.

Conclusions: In DD-CKD pts who remained on treatment for ≥2y, roxadustat maintained Hb ≥10 g/dL with minimal dose change and less need for rescue therapy, including RBC transfusion, than PBO.

Funding: Commercial Support - AstraZeneca; Astellas, and Fibrogen

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effects of Roxadustat in Patients with Dialysis-Dependent CKD (DD-CKD) Across All Baseline (BL) Hemoglobin (Hb) Values

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases Hb by stimulating endogenous erythropoietin synthesis and improving iron bioavailability. This pooled post hoc analysis evaluated the efficacy and safety of roxadustat in patients (pts) with DD-CKD across all available BL Hb values.

Methods: Pts were randomized to open-label roxadustat (n=1943) or epoetin alfa (EPO; n=1947) in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Across trials, BL Hb eligibility criteria were ≤10 g/dL at final screening, study drug dose was titrated to Hb 11±1 g/dL. Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy (IV iron, red blood cell [RBC] transfusion or ESA). Pooled post hoc subgroup analyses were performed by selected Hb values (g/dL: <8.0, ≥8.0–<9.0, ≥9.0–<10, ≥10.0) at BL (mean of up to 4 pre-randomization values) regardless of study rescue therapy use. Adverse events (AEs) were assessed.

Results: Pts study discontinuation rates were similar across all BL Hb ranges (Table). Pts with lower BL Hb had less time on dialysis (Table), suggesting pts incident to dialysis. At BL, pts with Hb ≤9 g/dL had the lowest weekly ESA doses, but by Weeks (wk) 49–52 their weekly ESA doses were highest (Table). Pts with BL Hb ≥8 g/dL received on average ~1 mg/kg/wk more roxadustat dose at wk 49–52 than pts with BL Hb <10 g/dL (Table). Rates of serious AEs (SAEs) and treatment-emergent SAEs per pt-exposure year were comparable for roxadustat vs EPO and appeared more common in pts with higher BL Hb (Table).

Conclusions: DD-CKD pts with more severe anemia at BL required more IV iron during the study. Roxadustat was effective and had comparable tolerability to EPO across all BL Hb studied.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

PO0454

Effects of Roxadustat in Patients with Non-Dialysis-Dependent CKD (NDD-CKD) Across All Available BL Hb Values

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases Hb by stimulating endogenous erythropoietin synthesis and improving iron bioavailability. This pooled post hoc analysis evaluated the effects of roxadustat in patients (pts) with NDD-CKD across all available BL Hb values.

Methods: Pts were randomized to double-blind roxadustat (n=2391) or placebo (PBO; n=1886) in 3 Phase 3 NDD-CKD trials (OLYMPUS, ALPS, ANDES). BL Hb eligibility criteria were ≤10 g/dL at final screening, study drug dose was titrated to Hb 11±1 g/dL. Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy (IV iron, red blood cell [RBC] transfusion or ESA). Pooled post hoc subgroup analyses were performed by selected Hb values (g/dL: ≤8.0, ≥8.0–<9.0, ≥9.0–<10, ≥10.0) at BL (mean of up to 4 pre-randomization values) regardless of study rescue therapy use. Adverse events (AEs) were assessed.

Results: Pts with lower BL Hb had higher study discontinuation rates and lower BL eGFR (Table). Across BL Hb ranges over Weeks (wk) 28–52, BL change in Hb and proportion of pts with Hb ≥10 g/dL were greater with roxadustat vs PBO (Table). Pts with BL Hb ≤8 g/dL were treated with ~2 mg/kg/wk more mean roxadustat dose at wk 49–52 than pts with BL Hb ≥10 g/dL (Table). IV iron or RBC transfusion need was less with roxadustat than PBO and with higher BL Hb (Table). Lower rates of serious AEs (SAEs) and treatment-emergent SAEs per pt-exposure year were observed with increased BL Hb (Table).

Conclusions: NDD-CKD pts with more severe anemia had worse kidney function, required more treatment including RBC transfusion and experienced more SAEs than pts with less severe anemia. Roxadustat improved anemia vs PBO across all BL Hb studied.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen
PO0455

Roxadustat in Elderly Patients with Anemia of CKD

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Background: Elderly patients with anemia of chronic kidney disease (CKD) typically have several comorbidities requiring polypharmacy, but slower drug metabolism than younger patients. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that promotes coordinated erythropoiesis and increased iron availability. We explored roxadustat treatment in elderly (≥65 years) patients in dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD populations.

Methods: Data were pooled from pivotal phase 3 studies of roxadustat vs placebo (stage 3-5 NDD-CKD) and vs epoetin alfa (DD-CKD). Data were analyzed for patients ≥65 and ≥65 years old. The primary endpoint in the overall trials was mean change from baseline in hemoglobin (Hb) in weeks 24–52, regardless of rescue therapy. Least square mean difference (LSMD) was determined between treatments. Secondary endpoints were transfusion rate per 100 patient-exposure years (NDD and DD) and change in mean IV iron use (DD). Adverse events were monitored during treatment + 28 days post treatment (NDD and DD).

Results: In NDD (N=4277) and DD (N=3590) populations, the majority were female (NDD) or male (DD) (Table). Baseline Hb levels were higher in elderly vs younger patients (Table). Age did not affect improvements in Hb, but mean CFB was greater in elderly vs younger in DD and NDD patients (Table). Transition rates were lower in younger vs elderly DD patients and in elderly vs younger NDD patients (Table). Trends in mean IV iron use were lower with roxadustat vs epoetin alfa and similar among age groups (Table). Roxadustat was well tolerated, regardless of age (Table).

Conclusions: Roxadustat was effective and well tolerated, regardless of age, in patients with anemia of CKD.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

Table: Baseline characteristics and safety endpoints

PO0456

Roxadustat Effectively Treats Anemia in Dialysis-Dependent CKD (DD-CKD) Patients with Ferritin ≥100 ng/mL

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD). We conducted 2 global phase 3, randomized, open-label, active-controlled, noninferiority trials (INOVOATE) comparing twice-daily oral dosing of VADA with the erythropoiesis-stimulating agent darbepoetin alfa (DA) in patients with anemia and incident (≥369) or prevalent (≥3554) dialysis-dependent (DD) CKD. Inclusion criteria: serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results of the INNOVOATE trials were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24–36) and secondary (wk 40–52) evaluation periods.

Methods: A total of 1958 patients received VADA and 1965 received DA. VADA treatment was associated with greater decreases in mean hepcidin and ferritin, and increases in TIBC from baseline to the primary and secondary evaluation periods (Table). Mean serum iron decreased more in the DA than the VADA group from baseline to wk 24–36 and 40–52. Oral and intravenous iron use was similar in the 2 treatment groups throughout both studies. Similar results were seen in the non-DD-CKD populations (PROTECT studies).

Results: The observed relative decreases in hepcidin and ferritin and the increase in TIBC are consistent with a VADA-induced facilitation of iron mobilization from intracellular stores that support erythropoiesis.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Table: Changes from baseline in iron-related parameters

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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182
PO0458

Associations Between Hepcidin and Laboratory Measures of Iron and Inflammation in Patients with Anemia and CKD Not on Dialysis in the Roxadustat Global Phase 3 Program

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Background: Hepcidin is the master regulator of iron homeostasis. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates coordinated erythropoiesis in part by reducing hepcidin. We investigated the associations between hepcidin levels and select laboratory parameters in anemic patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) in the roxadustat studies.

Methods: This analysis used data from 3 similarly designed pivotal phase 3 studies (OLYMPUS, ANDES, and ALPS) of roxadustat vs. placebo in anemic patients with stage 3-5 NDD-CKD. Quantiles of baseline BL) hepcidin levels and changes from baseline (CFB) in hepcidin were evaluated for associations with select labs at BL and changes at weeks 20-28. Multivariate regression to hepcidin was performed at BL and after treatment using full analysis set.

Results: 2717 patients were assessed (1630 roxadustat, 1087 placebo). BL hepcidin (range 7.0 to 808.2 µg/L) was analyzed by quintile regardless of treatment group. Patients with higher BL hepcidin were observed to have a lower hemoglobin (HB), lower eGFR, higher C-reactive protein (CRP), higher serum iron, higher ferritin, and lower total iron binding capacity (TIBC), and higher transferrin saturation (TSAT) compared to lower hepcidin groups (Table). Further analysis of these relationships using multivariate regression models with minimalized AIC score model selection criteria showed that hepcidin (log-transformed) was significantly associated with the following BL parameters (log-transformed) in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), eGFR(-), albumin(+), Hb(-). The mean (SD) CFB in hepcidin at week 24 was -23.1 (86.0) µg/L in the roxadustat group vs. +12.3 (87.8) µg/L in the placebo group. Hepcidin associations after treatment will also be presented.

Conclusions: Baseline hepcidin was strongly associated with iron parameters like serum ferritin but not other known factors, such as CRP, in NDD-CKD patients with anemia.

PO0459

Associations Between Hepcidin and Laboratory Measures of Iron and Inflammation in Incident Dialysis Patients with Anemia Enrolled in the Roxadustat Global Phase 3 Program

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Background: Hepcidin is the master regulator of iron homeostasis. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates coordinated erythropoiesis in part by reducing hepcidin. We investigated the associations between hepcidin levels and select laboratory parameters in incident dialysis (ID) patients with anemia.

Methods: This exploratory analysis used data from 3 similarly designed pivotal phase 3 studies (ROCKIES, HIMALAYAS, and SIERRAS) of roxadustat vs. epoetin alfa in ID patients with anemia (NDD-CKD) in the ROCKIES study (NCT02994652). Patients with higher BL hepcidin were observed to have a lower hemoglobin (HB), lower eGFR, higher C-reactive protein (CRP), higher serum iron, higher ferritin, lower total iron binding capacity (TIBC), and higher transferrin saturation (TSAT) compared to lower hepcidin groups (Table). Further analysis of these relationships using multivariate regression models with minimalized AIC score model selection criteria showed that hepcidin (log-transformed) was significantly associated with the following BL parameters (log-transformed) in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), eGFR(-), albumin(+), Hb(-). The mean (SD) CFB in hepcidin at week 24 was -23.1 (86.0) µg/L in the roxadustat group vs. +12.3 (87.8) µg/L in the placebo group. Hepcidin associations after treatment will also be presented.

Conclusions: Baseline hepcidin was strongly associated with iron parameters like serum ferritin but not other known factors, such as CRP, in NDD-CKD patients with anemia.

PO0460

Comprehensive Safety Profile of Vadadustat from Global Phase 3 Clinical Trials

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We pooled safety data from 4 global phase 3, randomized, open-label trials evaluating VADA vs darbeopoetin alfa (DA) in patients with dialysis- and non-dialysis-dependent CKD trials (INNO-VATE and PROTECT, respectively) who received DA dose of study drug. We summarized treatment-emergent adverse events (TEAEs) by MedDRA system organ class (SOC) and preferred term (PT). We extracted AEs of special interest (AESIs) using Standardized MedDRA Queries and analyzed as groups of PTs (medical topics).

Results: A summary of TEAEs by treatment group is provided (Table). The most common in the VADA and DA groups by SOC were infections and infestations (50.8%, 35.2%), metabolic and nutrition disorders (34.6%, 36.2%), and injury, poisoning and procedural complications (29.5%, 30.7%). The most common drug-related TEAEs in the VADA group were the PTs of diarrhea (2.2%) and nausea (1.2%), leading to study drug discontinuation in 0.4% and 0.2% of patients, respectively. The most frequent serious AEs (SAEs) in the VADA and DA groups occurred in the SOCs for infections and infestations (23.3%, 24.0%) and renal and urinary disorders (18.6%, 18.1%). TEAEs leading to death in the VADA and DA groups were cardiac arrest (1.7% in each group), end-stage kidney disease (1.8%, 1.3%), and cardio-respiratory arrest (0.9%, 1.0%). AESIs (>10%) in the VADA and DA groups were hypertension (18.0%, 21.0%), congestive heart failure (10.3%, 11.5%), and hyperkalemia (9.9%, 11.9%), all of which were more frequent with DA.

Conclusions: VADA exhibited a TEAE safety profile generally comparable to DA. Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.
cell carcinoma of the skin, cutaneously resected squamous cell carcinoma of the skin, or cervical carcinoma in situ. Malignancies are reported here as events per 100 patient-years (PY).

**Results:** In total, 3686 patients were exposed to VADA and 3687 to DA for a median of 36.7 wk (25%, 75th percentile range 31.9–91.7 wk) and 70.0 wk (39.9–102.1 wk); 54.9% vs 52.2% patients were exposed for <52 and 18.9% and 24.1% for ≥52 and <100 wk, respectively. Malignancies in the VADA and DA treatment groups were 2.1 events/100 PY and 2.7 events/100 PY, respectively (relative risk [RR], 0.81; 95% confidence interval [CI], 0.64–1.02). Specifically, malignancies in patients with NDD-CKD were 2.2 events/100 PY (RR, 0.89; 95% CI, 0.65–1.21), and in patients with PD CKD was 1.5 vs 2.4 events/100 PY (RR, 0.72; 95% CI, 0.50–1.03), for VADA vs DA, respectively. In both studies, no pattern was observed for any specific type of malignancy, including renal cell carcinoma in patients with PD or NDD CKD.

**Conclusions:** VADA was not associated with an increased risk of neoplasms compared with DA in patients with anemia and CKD.

**Funding:** Commercial Support - Akemia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

**Methods:** Here we describe the prespecified pooled analysis of the secondary safety endpoints of time to first thromboembolic event, including (1) any thromboembolic event (a composite of events of vascular access thrombosis, arterial thrombosis, deep venous thrombosis [DVT], and pulmonary embolism [PE]), (2) arterial thrombosis, DVT, or PE, and (3) venous thromboembolic events (DVT or PE).

**Results:** Of the 3923 patients randomized in the 2 INNO VATE trials, 309 were randomized to VADA (N=1557; 79%). Among patients receiving PD (VADA, N=152; DA, N=157), MACE included a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke, prespecified as a pooled event-driven analysis of both trials. As previously reported, the hazard ratio (HR) [VADA:DA] for MACE was 1.17 (95% confidence interval [CI], 1.01–1.36), which did not meet the prespecified noninferiority margin of 1.25.

**Conclusions:** In the phase 3 PRO2TECT trial in patients with anemia and DD-CKD, the rate of thromboembolic events was similar between the VADA and DA groups.

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PO0467

Renal Injury Biomarkers Are Elevated in Acute Hepatic Porphyria

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**Background:** Acute hepatic porphyria (AHP) is a group of rare genetic diseases caused by defects in enzymes in the heme biosynthesis pathway. Acute intermittent porphyria (AIP) is the most common subtype. In patients with AHP, accumulation of porphyrins in the blood can lead to acute attacks and long-term complications including hypertension and chronic kidney disease which is present in 30-60% of patients with biochemically active AIP. Chronic high excreters (CHE) are a group of patients that carry a genetic mutation and have elevated levels of ALA and PBG but are not experiencing acute attacks.

**Methods:** Proteomic analysis (Olink® platform) was used to measure 1196 proteins in 588 patients with AHP suffering from recurrent acute attacks as well as chronic kidney disease in patients with AHP. Two proteins with the largest effect sizes, kidney injury molecule-1 (KIM1; 3.4-fold; p-value= 8.0e-13) and matrix metalloproteinase-7 (MMP7; 5-fold; p-value= 1.5e-25) were previously described as biomarkers of renal injury. Three additional kidney injury biomarkers (neutrophil gelatinase-associated lipocalin, cystatin C (CST3) and chitinase-3-like protein 1) showed significant elevations in patients with AHP compared to controls (0.3-fold; p-value=0.034 to 0.001). KIM1, MMP7, and CST3 were also significantly elevated in CHE compared to controls.

**Conclusions:** Renal injury biomarkers may aid in diagnosing and managing kidney disease in patients with AHP suffering from recurrent acute attacks as well as chronic kidney disease.

Funding: Commercial Support - Ailylam Pharmaceuticals Inc.

PO0468

A Contemporary View of Erythropoietin-Stimulating Agent Switching: Determining a Dose Conversion Ratio (DCR) from IV Epoetin Alfa to IV PEG-Epoetin Beta and SC Epoetin Beta to Preserve Haemoglobin Concentration in Dialysis Patients

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**Background:** Recent studies, such as PIVOTAL, in haemodilution show the benefit of adequate iron repletion, including reduction in ESA dose. This study aims to determine the DCR to maintain Hb stability in a contemporary HD cohort, switch from IV epoetin alfa (Remicor®) to sc epoetin beta (Merocon®) or IV PEG-epoetin beta (Micrera®).

**Methods:** This observational study from a UK single-centre analysed HS stability and ESA requirements in 260 HD patients on IV epoetin alfa, who switched to sc epoetin beta (n=118) or IV PEG-epoetin beta (n=142). Data from a 3 mth Baseline period were compared to a 9 mth post-switch Evaluation period. The DCRs were calculated using Evaluation dose / Baseline dose. The target Hb was 100-120g/L. Iron requirements were determined from TSAT, Ret-He and Ferritin.

**Results:** The mean Hb, Hb in target, ESA dose, frequency and DCR were: For IV PEG-epoetin-beta group 109g/L, 75%, 10418 iU/wk, 3/wk, at baseline;109g/L, 81%, 181mg/m2/wk, 1/mth, at evaluation; resulting DCR 1mcg:249iU. For sc epoetin beta 111g/L, 74%, 971IU/wk, 3/wk, at baseline; 111g/L, 88%, 7528 IU/wk, 2/wk, at evaluation; resulting DCR of 0.8. At these DCRs the Hb stability was maintained throughout the study.

**Conclusions:** Enhanced communication with non-dialysis patients about anaemia, as well as earlier detection and intervention with novel HIF-PH inhibitors, could lead to better anaemia outcomes.

PO0469

Anemia Care of Hemodialysis Patients: A National Study from Qatar

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**Background:** Anemia targets in dialysis patients is hard. Challenges like cost, compliance and erythropoietin stimulation agents (ESA) resistance can hamper anemia management. We established a new national anemia nurse manager model to improve care of anemia in dialysis patients in the State of Qatar. Key drivers of the model are summarized in Figure below. We studied the effects of this program in improving anemia care in hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0470

Contemporary Anemia Treatment in Prevalent Patients Undergoing Hemodialysis
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Background: Anemia treatment remains a major area of focus in the management of maintenance dialysis patients. We assessed hemoglobin (Hb) and erythropoiesis-stimulating agent (ESA) dosing among hemodialysis (HD) patients with records in CROWNWeb, a national reporting system that captures data from all prevalent patients undergoing maintenance dialysis, regardless of whether patients carry Medicare coverage. Methods: We analyzed United States Renal Data System Standard Analysis Files. For each calendar month from January 2015 to September 2019, we identified adult (age ≥18 years) patients who underwent HD during the entire month and whose CROWNWeb records included a valid measurement of single-pool Kt/V. In each patient-month, we identified Hb and ESA treatment (agent [epoetin alfa, darbepoetin alfa, or pegylated epoetin beta] and monthly cumulative dose). Subsequently, we tabulated the distribution of Hb in each month, incidence of 3-month and 6-month series with Hb <10.0 g/dL; utilization of ESAs, overall and by agent; and mean weekly ESA dose, by agent.

Results: Among 878,883 patients in the study period, 7.2% of patient-months had Hb <9.0 g/dL, 15.2% had Hb 9.0-9.9 g/dL, 35.3% had Hb 10.0-10.9 g/dL, 28.5% had Hb 11.0-11.9 g/dL, and 13.9% had Hb ≥12.0 g/dL. The prevalence of Hb <9.0 g/dL was relatively higher with age ≥18-44 years, Black race, and female sex. Among all 6-month series of Hb measurements, 5.8% had Hb <10.0 g/dL for 3 consecutive months and only 2.0% had Hb <10.0 g/dL for 6 consecutive months. Approximately 76% of patients received an ESA in each month. In 2019, 34% used epoetin alfa, 9% used darbepoetin alfa, and 33% used pegylated epoetin beta. Mean (median) weekly doses were 10,562 (7727) IU for epoetin alfa, 35.9 (23.0) mcg for darbepoetin alfa, and 33.6 (23.0) mcg for pegylated epoetin beta.

Conclusions: Between 2015 and 2019, despite substantial flux in the mix of ESAs used, distributions of hemoglobin and ESA doses among patients undergoing HD were stable, with only a small percentage of patients experiencing persistently low hemoglobin.

Funding: Commercial Support - Amgen Inc.
PO0473

The Effect of a Patient Blood Management Program on Renal Outcome in Patients with CKD

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Background: Transfusion burden is high in CKD patients to treat anemia. However, transfusions had risks including volume overload, alloimmunization, blood stream infections and thromboembolism. We evaluated the effect of a monitoring program to identify appropriate transfusions in CKD patients.

Methods: Based on the guidelines of the Korean Society of Blood Transfusion, Korea University Anam Medical Center developed a verification program to assess the adequate indication of transfusion (patient blood management(PBM)) in August 2018. We analyzed 1,192 CKD patients admitted to the department of nephrology from August 2016 to July 2020. Patients were divided into two groups: patients who admitted before the implementation of PBM (pre-PBM(n=592)) and after the implementation of PBM (post-PBM(n=600)).

Results: The amount of blood transfused was 628 units in pre-PBM group and 443 units in post-PBM group. The patients who received more than 2 units was significantly lower in post-PBM group (20.1% vs. 13.5%, p=0.002). There were no differences in the administered doses of erythropoietin and iron between the groups. Although hemoglobin(Hb) (10.5±2.0 vs. 10.3±2.2) were not different between the two groups at admission, Hb levels were significantly lower in post-PBM group at discharge (10.4±1.8 vs. 10.1±2.0, p=0.010) and 6 months after admission (11.5±1.9 vs. 11.1±2.0, p=0.007). Kaplan-Meier analysis showed a survival benefit of CKD progression (≥50% increase in serum creatinine) (p=0.001) and percutaneous coronary intervention (p=0.030) in the post-PBM group. The incidence of end stage kidney disease or mortality was not different between groups. In multivariate analysis, PBM was associated with lower risk for CKD progression (HR of 0.587; 95% CI 0.416-0.830).

Conclusions: Patient blood management program may reduce inappropriate RBC transfusion. Implementation of PBM was associated with lower risk of CKD progression in hospitalized CKD patients.

PO0474

Ferric Pyrophosphate Citrate (Triferic® AVNU): Alternate Intravenous Dosing Strategies Compared to Continuous Infusion over 3 Hours

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Background: Ferric pyrophosphate citrate injection (FPC-IV) is an iron replacement product to maintain hemoglobin by intravenous infusion over 3 to 4 hours. The aim of this study was to investigate FPC-IV pharmacokinetics and confirm safety of alternate dosing strategies.

Methods: An open-label, randomized, multiple period single dose study was conducted in 23 CKD-3HD patients to establish the equivalence of doses between FPC-IV as a 3-hour infusion using the on-machine syringe pump and 5 alternate dosing strategies. The treatments were A) Baseline FPC-IV 6.75 mg Fe/3 hours (approved rate); B) FPC-IV 3.38 mg Fe bolus injections at t=0 and t=3 hours; C) FPC-IV 6.75 mg Fe bolus injection at t=0 hours over 0.5 - 5 min. and D) FPC-IV 2.25 mg Fe bolus injections at t=0, t=1.5 and t=3 hours and E) FPC-IV 6.75 mg Fe by infusion using a spring-driven syringe pump with flow restrictive tubing to deliver 2 ml/hr. Blood samples were obtained to assess total iron (FeTOT), transferrin bound iron (TBI), transferrin saturation (TSAT) and iron binding capacity (TIBC).

Results: The results for TSAT (Fig.1) track the administration group. FPC-IV was generally well tolerated in all treatments. There was transient flushing and abdominal discomfort of mild to moderate severity associated with treatment C (bolus injection of FPC over 0.5-5 min.) experienced by 15 of 16 patients. All symptoms spontaneously resolved over 2 to 5 minutes and no adverse events or intolerance was reported with any other treatment.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion using a spring-driven pump (FP) over 71 to 195 minutes. The increment in sFe in this study is compared to the dialysate and IV FPC infusions over 3 hours in Figure 1. The sFe was rapidly cleared with no increase in pre-dialysis sFe. FPC-IV was well tolerated with no reported adverse events.

Funding: Commercial Support - Rockwell Medical Inc.

PO0475

Ferric Pyrophosphate Citrate (Triferic® AVNU) Injection: Alternate Intravenous Dosing Using a Spring-Driven External Infusion Pump

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Background: Ferric pyrophosphate citrate injection (FPC-IV) is an iron replacement product to maintain hemoglobin by intravenous infusion (IV) over 3 to 4 hours. Some hemodialysis (HD) centers cannot use HD system syringe pumps for drug administration. We investigated the use of a spring-driven syringe pump to infuse FPC-IV into the pre- or post dialyzer blood line.

Methods: An open-label, study was conducted in 12 HD patients at 6 treatments. FPC-IV (6.75mg Fe/4.5 mL) was drawn up into 20 ml syringes. The syringe was attached to a flow-restrictor tubing 2 ml/hr (nominal rate) and then attached to the the pre-Dialyzer blood line port or to the venous drip chamber. The syringe was placed in the chamber of the FreedomEdge® Pump (FP) and the pump activated. Blood for serum iron (sFe) and transferrin saturation (TSAT) was collected pre-hemodialysis and immediately post infusion.

Results: FP Delivery of FPC took an average of 134 ± 31.7 minutes (Range 71 to 195 min). The mean increment in sFe pre- to post infusion was 202 ± 73.7 μg/dL. The pump set up, including loading the syringe, took an average of 109 ± 42.7 sec (Range: 48 to 251 sec.). The incremental sFe in this study is compared to the dialysate and IV FPC infusions over 3 hours in Figure 1. The sFe was rapidly cleared with no increase in pre-dialysis sFe. FPC-IV was well tolerated with no reported adverse events.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion using a spring-driven pump (FP) over 71 to 195 minutes. The increment in sFe is slightly greater than the 3 or 4-hour FPC infusions due to the shorter administration time. A spring-driven infusion pump to administer FPC IV is well-tolerated and a suitable alternative to use of the Hemodialysis machine syringe pump.

Funding: Commercial Support - Rockwell Medical Inc.
PO0476

Association Between Serum Indices of Iron Metabolism and Cardiovascular Morbidity in Patients with Pre-Dialysis CKD

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Background: The optimal ranges of serum iron markers are uncertain in predialysis chronic kidney disease (CKD) patients. Therefore, we aimed to investigate the association between serum indices of iron metabolism and the incidence of CVD events in patients with predialysis CKD using the CKD-Japan Cohort (CKD-JAC) data.

Methods: We prospectively followed 1,550 CKD patients aged 20-75 years with an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m2 for a mean of 4.21 years. We set serum transferrin saturation (TSAT) and ferritin levels as the main exposures to be tested. Our main outcome measures were any of the CVD events including congestive heart failure (CHF) identified at each facility and adjudicated by the independent cardiac function evaluation committee. Multivariable Cox proportional hazards regression models were employed to examine the association between serum TSAT or ferritin levels with time to events. All models were stratified by facilities and adjusted for potential confounders. We also applied the multivariable fractional polynomial interaction (MFPI) approach to investigate whether serum TSAT or ferritin levels are the effect modifier of the association between iron supplementation and the outcomes.

Results: In the overall cohort, 268 (13.4 %) patients developed CVD events (including 97 CHF) during the follow-up period (26.6 events/1000 person-year). The incidence rate of CVD events was the highest in the TSAT < 20% category (33.0 events/1000 person-year). Compared to patients in the TSAT > 40% category, those in the TSAT > 20% category demonstrated an increased risk of CVD events (adjusted hazard ratio [AHr]: 1.06-3.26) and CHF events (AHr: 2.82, 95% CI: 1.15-6.89), respectively. There was no association between serum ferritin levels and the risk of CVD or CHF events. MFPI analyses showed a reduced risk of CVD in patients receiving iron supplementation only in patients with TSAT < 20% (P for interaction=0.02).

Conclusions: Maintaining TSAT > 20% could be effective to reduce the risk of developing CVD events (especially CHF) in patients with predilation CKD. Our analyses also suggest that iron-deficient patients with predilysis CKD may benefit from iron supplementation for reduced risk of CVD events.

PO0477

Serum Erythroferrone and Serum Hepcidin 25 Are Associated with CKD

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Background: Erythroferrone is a recently discovered hepcidin suppressor expressed in erythroblasts in response to erythropoietin (EPO) with the downstream effect of increased iron availability. In light of the central role of hepcidin-25 in the pathogenesis of anemia, we determined serum erythroferrone, serum hepcidin-25, the hepcidin/ferritin ratio, and the ESA hyporesponsiveness index (ERI) in different stages of chronic kidney disease (CKD).

Methods: Erythroferrone was determined by ELISA in 602 CKD patients (97 CKD 3-4, 220 CKD 5 non-dialysis patients, 76 prevalent peritoneal dialysis (PD) patients, and 209 prevalent hemodialysis (HD) patients). The ERI was calculated as follows: ESA dose (international units) per kg haemoglobin level (g/L) per week. Differences in levels of erythroferrone (ng/mL), hepcidin-25 (nmol/L), the ferritin ratio, and ERI between stages of CKD were assessed by non-parametric ANOVA.

Results: Serum erythroferrone and serum hepcidin-25 increased with increasing CKD stage and were higher in patients with CKD 5, in PD patients, and in HD patients as compared to patients with CKD 3-4 (Figure A, B). When levels of hepcidin-25 were corrected for serum ferritin levels (hepcidin/ferritin ratio), only patients in CKD 5 had higher levels as compared to patients in CKD 3-4 (Figure C). Estimated ERI was higher in CKD 5 and HD patients as compared to CKD 3-4 patients (Figure D). The high tertile of erythroferrone in CKD 5 was associated with worse clinical outcome. No significant association with clinical outcome was observed in other cohorts.

Conclusions: Serum erythroferrone, serum hepcidin and ERI were linearly associated with deteriorating renal function. We found significant association of erythroferrone to all-cause mortality in CKD 5 patients.
Hypersensitivity Reaction to Epoetin-Alfa: A Therapeutic Challenge

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Introduction: Use of erythropoiesis stimulating agents (ESA) prevent the need for recurrent blood transfusions in patients with advanced kidney disease. Rarely, patients can have allergic reactions to the ESA components which can range from pruritic rash to fatal angioedema. We report a case of delayed-type hypersensitivity reaction (DTH) due to epoetin-alfa (EPO). Cross-reactivity between molecular structures of various agents raises a therapeutic challenge.

Case Description: A 78 year old man with anemia in the setting of chronic kidney disease stage 4 secondary to diabetes mellitus was initiated on EPO 10,000 units per month. He developed an urticarial rash in the back and chest after the first dose, which gradually worsened after receiving the second dose. Review of recent history was negative for any other new medication or chemical exposure. He underwent skin biopsy which showed dermatitis with eosinophils supporting a drug reaction. EPO was discontinued with resolution of the rash. Given known risk of cross-reactivity between various ESA molecules, he was subsequently referred to an allergist for desensitization protocol, followed by successful re-introduction of ESA therapy.

Discussion: Currently, ESA remains the treatment of choice for anemia of kidney disease, in order to limit need for blood transfusions. ESA-related DTH reactions can be due to excipients such as polysorbate, as well as the structural subunits of erythropoietin. Cross-reactivity has been reported between different ESA structures, which raises a therapeutic challenge in the care of such patients. Clinicians should consider desensitization, which can lead to successful re-introduction of ESA therapy.

PO0479

PO0480

An Unusual Cause of Anemia: Duodenal Compression by Polycystic Kidneys


Introduction: We report a rare case of gastrointestinal bleeding due to extrinsic compression and shearing of bowel in a patient with autosomal dominant polycystic kidney disease (ADPKD).

Case Description: A 52-year-old male presented with progressive dyspnoea and melaena over one week. He was noted to have an eGFR of 9 ml/min/1.73 m², giant polycystic kidneys and a family history of ADPKD. A diagnosis of ADPKD was made and he was commenced on peritoneal dialysis. He was noted to have mirtal regurgitation and hypertension. His haemoglobins at presentation was 39 g/L and his blood film revealed ovalocytes, without evidence of haemolysis. Haematinics were suggestive of iron deficiency. While uraemic at presentation, he had no other notable risk factors for bleeding. Upper GI endoscopy and colonoscopy were both unremarkable. He was treated with red cell transfusion, intravenous iron and commenced on an erythropoiesis-stimulating agent. He presented on four subsequent occasions over an 8 month period with recurrence of severe anemia and melaena. A capsule endoscopy suggested bleeding at the duodenal-jejunal flexure, however no source was visualised. The cause of the bleeding was revealed by double balloon enteroscopy which demonstrated extrinsic compression of the scope at D3. Review of imaging confirmed this was due to a large right renal cyst. Ongoing tranexamic acid and lanreotide treatment has reduced the frequency of bleeds.

While a nephrectomy would potentially provide a definitive solution to the underlying cause, this carries substantial risk and would need to be carefully coordinated with his mitral valve repair.

Discussion: While peptic ulcer disease is slightly increased in ADPKD, this is the first description of mechanical trauma to bowel by polycystic kidneys resulting in severe recurrent GI bleeding. Teaching points 1. Giant polycystic kidneys can rarely compress small bowel and cause GI bleeding 2. Correlation of advanced endoscopy such as double balloon enteroscopy with radiology may be required to make the diagnosis 3. Tranexamic acid and lanreotide may reduce bleeding.

PO0481

Targeted Literature Review (TLR) Exploring Adherence to Treatments, with Potential to Extrapolate to Patients with Anemia of CKD

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Background: Adherence to long-term treatment for chronic diseases, e.g. anemia of CKD, is problematic. Adherence to a patient’s preferred treatment is critical to successful CKD management. We explored: availability of published best practice guidance for long-term disease; how analog scenarios from healthcare teams and patients provide learning about treatment adherence and persistence; patient preferences; and how to measure adherence-related outcomes.

Methods: We conducted a TLR of analog scenarios where an oral therapy was introduced in a setting with injectable/subcutaneous therapy as standard of care. Embase and Cochrane searches included administration route, dosing frequency and titration, from 2016–2020. Searches were limited to literature reviews and clinical guidelines for adults with chronic disease from 10 countries.

Results: Of 1421 papers identified, 85 were relevant. Inspection of these papers revealed that non-adherence may be intentional or non-intentional, and can be linked to numerous factors, e.g. polypharmacy, treatment regimen complexity, number of daily tablets, lengthy treatment duration, and patient beliefs about treatment. Intentional non-adherence may link to patients’ motivations/beliefs, and non-intentional non-adherence may link to patients’ skill/ability to take a medicine. Regimen complexity can be influenced by drug dosage form, product characteristics, dosage schemes, specific additional instructions (e.g. fixed-time daily dosing), patient characteristics and administration errors. Discrete choice experiments and conjoint analyses provide robust means of measuring patient preferences, but evidence is conflicting of preference for injectable vs oral treatments, which is relevant to anemia of CKD management. Accurately documenting evidence of medication ingestion/administration is difficult. While several methods exist for assessing treatment adherence and persistence, no gold standard was identified.

Conclusions: In a competitive treatment setting, there remains significant opportunity to support patients in their treatment choice. Identifying best practice models of treatment adherence, persistence and measuring patient outcomes may prove important for differentiating between treatment options.

Funding: Commercial Support - Astellas Pharma Inc.
Iron-Related Outcomes in Patients with Non-Dialysis-Dependent CKD Randomized to Vadadustat vs. Darbepoetin Alfa

Methods: We conducted 2 global phase 3, randomized, open-label, sponsor-blind, active-controlled, noninferiority trials (PROTECT) comparing once-daily oral dosing of VADA with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa (DA) in 1751 patients with non–dialysis-dependent CKD (NDD-CKD) not previously ESA treated and in 1725 NDD-CKD patients previously ESA treated. Inclusion criteria included serum ferritin ≥100 mg/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24–36) and secondary (wk 40–52) evaluation periods (PEP and SEP).

Results: A total of 1741 patients received VADA and 1735 received DA. VADA treatment was associated with greater decreases in mean ferritin, ferritin, and TSAT, and increases in TIBC from baseline at PEP and SEP (Table). A small increase in serum iron was seen in the VADA group as was a decrease in the DA group from baseline to PEP and SEP. Oral and IV iron use was similar in the 2 treatment groups throughout both studies.

Conclusions: Treatment with VADA resulted in relative decreases in hepcidin and ferritin and increases in TIBC and serum iron. Decreases in TSAT should be interpreted in light of a greater increase in TIBC than that of serum iron. These changes are consistent with a VADA-induced increase in iron mobilization from extracellular stores that support erythropoiesis.

Funding: Commercial Support - Akemia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

IL-6 Inhibitor Ziltivekimab Increases Serum Hemoglobin and Iron Biomarkers in Patients with CKD Stage 3–5: A RESCUE Trial Analysis

Methods: Changes in anemia markers from baseline (BL) to Week 12 were assessed in pts (CKD stage 3–5, high-sensitivity C-reactive protein ≥2 mg/L) treated with ziltivekimab 7.5, 15 or 30 mg vs placebo (PBO). The intention-to-treat population was analyzed using a mixed model for repeated measurements (no adjustment for multiplicity). Analysis by BL Hb level (<11 or ≥11 g/dL) was conducted.

Results: In the RESCUE trial overall, mean age was 66 years, median Hb 12.5 g/dL at BL (N=198, ziltivekimab; N=66, PBO). Ziltivekimab increased Hb from BL to Week 12 vs PBO (p<0.001 for each dose; Figure/Table), with numerically greater increases with ziltivekimab vs PBO in pts with BL Hb <11 g/dL than pts with BL Hb ≥11 g/dL (Table). Ziltivekimab increased serum iron levels (p<0.0001), total iron-binding capacity and transferrin saturation (both p<0.01) vs PBO. No major safety concerns were reported.

Conclusions: Ziltivekimab improved levels of Hb, serum iron and other iron biomarkers vs PBO in pts with CKD stage 3–5. By reducing inflammation and improving functional iron deficiency, ziltivekimab may improve anemia in pts with CKD.

Funding: Commercial Support - Novo Nordisk

Sodium-Glucose Cotransporter 2 Inhibitors and Anemia Among Diabetic Patients in Real Clinical Practice

Methods: This is a retrospective cohort study. Inclusion criterion was diabetics who visited our outpatient clinic from January 2019 to August 2020. Exposure of interest was the use of SGLT2 inhibitors. Outcomes were hemoglobin levels. For the cross-sectional analyses, restrictive regression models were fitted with restricted cubic splines to investigate the association between hemoglobin levels and estimated glomerular filtration rate (eGFR) for users and non-users of SGLT2. For the case-control study, cases (anemia defined as hemoglobin <12 g/dL for men, <11g/dL for women or the use of erythropoiesis stimulating agents) and controls were matched by age, sex, and eGFR.

Results: Among 2063 diabetics, 723 were on SGLT2. In the cross-sectional analyses, hemoglobin levels were higher among SGLT2 users compared with non-users at eGFR >15 ml/min/1.73m². For the case-control study, 197 cases and controls were

Elevation in Red Cell Distribution Width (RDW) Is a Risk Factor for Future Hyponatremia and Hypokalemia

Methods: A hospital-wide study with all the laboratory data for a period of 4 years and 2 months was conducted. First, for each patient, hemoglobin (Hb) measurements of the initial 365 days were retrieved and the maximum RDW was obtained. Then the latest and 2 months was conducted. First, for each patient, hemoglobin (Hb) measurements of the initial 365 days were retrieved and the maximum RDW was obtained. Then the latest Hb and RDW measurement, were obtained. Prevalence and odds ratio (OR) of hyponatremia and hypokalemia were calculated for each quartile of RDW. Statistical analyses were performed with R 3.6.0 on Ubuntu and Microsoft Excel.

Results: A total of 5,537 patients were included in the study. Hb ranged from 7.7 to 20.2 (median 13.4) g/dL, MCV 55.7-124.5 (93.1) fL, and RDW 10.1-34.6 (12.7)%.

Conclusions: Elevation in RDW is a risk factor for future development of hyponatremia and hypokalemia
matched. Conditional logistic regression showed that the use of SGLT2i was associated with significantly lower prevalence of anemia (OR: 0.35 [0.21-0.58]). Adjusted mean differences (95% CIs) in hemoglobin levels between users and propensity score-matched non-users of SGLT2i were 0.7 (0.3-1.0) g/dL at 6 months. Among SGLT2i users, odds of increase in 6-month hemoglobin were similar across eGFR categories except for eGFR <15 mL/min/1.73m².

Conclusions: The use of SGLT2i was associated with higher hemoglobin levels and lower prevalence of anemia in real clinical practice.

PO0487
ASCEND-TD: A Randomized, Double-Blind, Active-Controlled Study of Daprodustat Administered Three Times Weekly in Hemodialysis Patients Daniel W. Covve,1 Ajay K. Singh,2 Renato D. Lopes,3 Christine K. Bailey,4 Tara L. Dimino,5 Chun Huang,6 Jeffrey J. Connaire,7 Anjay Rastogi,8 Sung guyn Kim,9 Marcelo Orias,10 Sapna Shah,11 Vickas Patel,12 Alexander R. Cobitz,13 Christopher Thomas,14 Division of Nephrology, Washington University School of Medicine, St. Louis, MO; 1Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; 2Duke Clinical Research Institute, Duke Health, Durham, NC; 3GliazoSmithKline, Collegeville, PA; 4Davita Clinical Research, Minneapolis, MN; 5Division of Nephrology, Department of Medicine, UCLA, Los Angeles, CA; 6Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea; 7Sanatorio Allende, Cordoba, Argentina; 8King’s College Hospital, London, United Kingdom; 9University of Würzburg, Würzburg, Germany.

Background: Daprodustat (dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for the treatment of anemia of chronic kidney disease (CKD). This study evaluated the efficacy and safety of daprod administered three-times-weekly (TIW) vs recombinant human erythropoietin (rEPO) for in-center prevalent hemodialysis (HD) patients.

Methods: This double-blind study (NCT03400033) randomized (2:1) HD patients with a baseline hemoglobin (Hb) of 8–11.5 g/dL already on rEPO to daprod TIW (n=270) or rEPO (n=137) for 52 weeks. A dosing algorithm aimed to maintain Hb between 10–11 g/dL. The primary endpoint was a mean change in Hb in the evaluation period (EP; Weeks 28-52). The principal secondary endpoint was the median monthly intravenous (IV) iron dose. Other secondary endpoints included blood pressure (BP) and Hb variability.

Results: Baseline characteristics in 407 randomized patients were balanced between the daprod and rEPO groups. Daprod TIW was non-inferior to rEPO for mean change in Hb (model-adjusted mean treatment difference [dapro-rEPO] -0.05; 95% CI: -0.21, 0.10). In the EP, mean (SD) Hb was 10.45 (0.549) g/dL and 10.51 (0.849) g/dL for daprod and rEPO groups, respectively. However, 80.0% in the daprod group were responders (mean %Hb during EP in the analysis range [10–11.5 g/dL]) vs 63.6% in the rEPO group, with a difference of 15.6% (one-sided nominal p=0.0007 after adjustment for regression). Mean monthly IV iron dose was not statistically significantly lower with daprod vs rEPO. While fewer BP elevations occurred with daprod vs rEPO (one-sided nominal p=0.0093), the overall effect of daprod on BP was similar to rEPO. In general, safety findings were comparable between treatment groups, with the incidence of treatment-emergent adverse events similar between daprod (75%) and rEPO (79%).

Conclusions: Dapro was non-inferior to rEPO in Hb response and was well-tolerated. Daprod administered TIW using the protocol employed in this study is a viable alternative to rEPO in prevalent HD patients with anemia of CKD.

Funding: Commercial Support - GliazoSmithKline

PO0488
Stabilization of Hypoxia-Inducible Factors Leads to Profound Epigenetic Changes in Primary Human Tubular Cells René Krüger, Mario Schiffer, Johannes Schödel, Stephanie Naas, Universitätshôpital Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany.

Background: Pharmacological stabilization of hypoxia-inducible factors (HIFs) to induce erythropoietin expression presents a novel therapeutic approach to treat patients with anemia of ESRD. Whereas the transcriptional activity of HIFs on the cellular level is well studied, insights in HIF-mediated alterations at the epigenetic level remain limited. The epigenetic landscape determines cellular identity and may be shaped by environmental factors such as hypoxia via HIF. In this study, we aim at generating a genome-wide atlas of the tubule-specific chromatin landscape while investigating the epigenetic plasticity of regulatory DNA elements provoked by HIF stabilization.

Methods: Primary tubular cells (PTC) were isolated from tumor nephrectomy specimens. We performed unbiased analyses of chromatin structure and accessibility using the undy Method (ATAC-Seq) and Chromatin Immunoprecipitation DNA-Sequencing (ChiP-seq), respectively. These epigenetic data sets were complemented with transcriptome information gained by RNA sequencing.

Results: ATAC-seq data generated in PTC obtained from four different individuals were combined to create a genome-wide landscape of chromatin accessibility comprising approx. 110 000 consensus regions. We validated cellular identity by benchmarking these sites against publicly available epigenomic data sets provided by ENCODE. Further characterization of chromatin activity was achieved by integration of ChiP-seq data for the histone mark H3K27ac. Pharmacological stabilization of HIF resulted in a remarkable change of chromatin accessibility yielding several hundred differentially open regions. Alterations of the chromatin coincided with HIF-binding events and HIF-mediated changes in mRNA expression suggesting a functional role for HIF in shaping chromatin accessibility in renal tubular cells.

Conclusions: Our genome-wide atlas of chromatin accessibility and activity in primary tubular cells represents a valuable reference data set for the investigation of tubule-specific features. Furthermore, our comprehensive approach allows for in-depth analysis of favourable as well as adverse epigenetic effects of HIF stabilizers in human tubular cells.
Triferic (Ferric Pyrophosphate Citrate, FPC) Maintains Hemoglobin and Reduces Total IV Iron Requirement: Results from a Mid-Sized Dialysis Organization (MDO) Pilot Observational Analysis

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Background: Triferic is approved as an iron (Fe) replacement product to maintain hemoglobin (Hb) in adult patients (pts) receiving chronic hemodialysis (HD). Randomized clinical trial data have demonstrated that FPC maintains Fe stores and Hb while reducing IV Fe usage with a safety profile similar to placebo. We now report the first 8 mos of an independent MDO’s experience using FPC for all HD patients (pts) during a pilot implementation at 14 clinics.

Methods: FPC was added to centrally delivered liquid bicarb to provide 110 µg Fe/L dialysate. All patients received FPC at each HD. Anonymized prospective data were provided between Sep 2020—Apr 2021. Clinics added FPC into their anaemia mgmt. practices per existing protocols and standards of care (SoC). Supplemental IV Fe, up to a max of 1000 mg Fe/mth, was administered according to a protocol based on serum ferritin and TSAT values. At baseline, the av. utilization of IV Fe was 197 mg/pt/mo. During the first 3 mos of FPC, clinics saw a modest 23% reduction of IV Fe (151 mg/pt/mo). A new Fe mgmt. protocol was released specifically designed to guide IV Fe use in conjunction with FPC; this was adopted by 9 clinics while 5 clinics chose to maintain their SoC.

Results: Within 3 mos of initiation of the new protocol, Fe utilization in this group decreased by 81%, conversely Fe utilization increased by 19% in the SoC group. During this period, Hb remained stable in both groups (+/- 0.2 g/dL from baseline). Concurrent with these changes Micrera® (-epoetin beta) dose remained stable in the SoC group but was reduced 37% (from post-adoption baseline) in the new group.

Conclusions: Additional clinics continued to adopt the new protocol over time. Taking into account the staggered adoption of the protocol, after 8 mos, the aggregate Fe utilization across all 14 clinics was reduced by 51% and trending lower. Micrera dose was stable (decreased 5%) and Hb remains stable. This observational study demonstrates that FPC is a well tolerated replacement for IV Fe when administered to all patients in a HD unit. The findings of this real-world observational study align with pivotal clinical trials and previously reported real-world evidence in terms of reduction of IV Fe use and maintenance of Hb.

Funding: Commercial Support - Rockwell Medical
Conclusions: We have shown the potential of our pipeline for image curation, and segmentation and sub-characterization of renal histologic primitives.

Funding: NIDDK Support

Results: At a total pump flow rate of 45.3 mL/min, 17.7 mL/min (± 5.08 mL/min), 12.9 mL/min (± 2.7 mL/min) and 7.6 mL/min (± 2.5 mL/min) recirculated in the bloodstream. In the MPS, average daily filtrate output was 0.016 mL/min, filtration of FITC-HSA in the MPS was over 90%, and glucose output in the filtrate supported PCT reabsorption. Confocal images displayed cell type-specific protein expression.

Conclusions: Filtering of HSA, glucose reabsorption, and marker expression in the MPS indicates a physiological representation of renal filtration and reabsorption in a human glomerulus and PCT. Our glomerulus and PCT MPS is a relevant preclinical tool for testing drug candidates for kidney toxicity.

Funding: NIDDK Support

Renal Proximal Tubule Chip (RPTC) for Disease Modeling and Drug Toxicity Testing

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Background: Tissue chips are an emerging technology in disease modeling and screening therapeutics to address discrepancies between animal models and human clinical trials. They utilize tissue engineered, fluid mechanics, and biomaterials to replicate in vivo architectures and functions of complex organs and tissues. For the renal proximal tubule (PT), there are currently limited options in terms of human cell types, scalable platforms for evaluation of drug toxicity, and tissue engineered solutions where the complexity of the PT is accurately modeled.

Methods: We developed both 2D and 3D versions of the RPTC which incorporates immortalized human renal PT epithelial cells (hRPTEC-TERT1) under static and perfused conditions (i.e. physiological pressure, shear stress, and stretch). Additionally, we have begun generating peritubular vascular networks using a co-culture of human umbilical vascular endothelial cells (HVECs) and human dermal fibroblasts (HDFs) in gelatin methacryloyl (GelMA). These models were then used to investigate the effect of pressure and flow on nephrotoxicity by introducing drugs with known levels of toxicity. Our initial evaluations have been limited to non-invasive measurements such as transepithelial electrical resistance (TEER) and pro-inflammatory soluble factors, and ICC.

Results: Compared to static controls, hRPTEC-TERT1 subjected to fluid shear demonstrate that culture under physiologically relevant forces results in cytoskeletal reorganization, establishment of barrier function (adherens and tight junctions) and increased expression of transporters like aquaporin 1 and mechanosensors like rat-tubulin. Additionally, noninvasive readouts such as TEER indicate the greater integrity of the renal proximal epithelium. Lastly, after 7 days, we can form dense microvascular networks to mimic the surrounding peritubular capillary networks which can actively reabsorb solutes from the glomerular filtrate. This network will enable us to test drugs in an environment where both reabsorption and secretion functions of the tubule are replicated.

Conclusions: These results provide preliminary evidence of our ability to subject hRPTEC-TERT1 to in vivo like flow conditions and demonstrate that replication of biomimetic forces from fluid shear, significantly enhances the relevant features of an in vivo-like phenotype which enhances the relevance of our in vitro models.

Funding: NIDDK Support

PO0495

Modeling Ischemia-Reperfusion in a High-Throughput Tubular/ Microvascular Co-Culture-on-a-Chip

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Background: Ischemia-reperfusion (IR) is a major cause of acute kidney injury (AKI). IR involves a period of inadequate perfusion that depletes highly metabolic kidney epithelia of nutrient and waste exchange impacting tissue structural integrity.

Methods: We demonstrate the potential of the PREDICT96 (P96) platform as a tool for examining tubule cell responses to IR. The oxygen-impermeable construction and robust pumping capabilities of P96 enable comparison of simulated IR and control conditions on a single culture plate. Here, primary human renal proximal tubule epithelial cells and human microvascular endothelial cells were cultured in adjacent microfluidic channels for 5 days under physiological fluid shear (0.07 Pa) to establish confluent layers. Subsequently, a portion of the tissue replicates underwent simulated IR consisting of 3 days of static conditions followed by 2 days of physiological flow. Transepithelial electrical resistance (TEER) was measured daily, and all tissues were fixed after 10 days in culture for structural characterization via immunofluorescence confocal microscopy.

Results: TEER measurements highlighted a transient increase in barrier function (cultures control tissues) in response to the onset of ischemia, followed by a reduction in integrity over subsequent days that persisted through reperfusion. IR tissues exhibited primary cilia that were on average less abundant but roughly double the length of those exhibited by control tissues. This is consistent with previous observations of cilia lengthening among IR-injured kidney epithelia in vivo. IR tissues also displayed nuclear staining for β-catenin suggestive of a proliferative response to injury.

Conclusions: The described model has significant potential to clarify mechanisms of IR injury in the kidney.

Funding: Other U.S. Government Support

PO0492

A 3D Vascularised Tubule Model Improves the Phenotype of Cultured Cells

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Background: Modelling proximal tubule physiology and pharmacology is essential for mechanistic studies and drug discovery. As a consequence, a plethora of models have been developed. Despite this no comparative study between monocultures, co-cultures and 3D models has been reported. In this study we aimed to understand the differences of proximal tubule epithelial cells (PTECs) and glomerular endothelial cells (HGECS) alone or in co-culture when grown in static non-coated, static matrix-coated and 3D flow matrix-coated conditions.

Methods: We cultured PTECs under physiological flow in a 3D channel embedded within an engineered extracellular matrix (ECM) that is colocalised with an adjacent channel lined with HGECS to mimic a peritubular capillary. After a period of maturation under continuous flow, both cell types were harvested for RNAseq analyses.

Results: Our results revealed that PTECs' transcriptional profile is highly dependent on the matrix on which these cells are cultured, as well as the application of flow. Endothelial cells however demonstrated greater phenotypic plasticity, being affected by matrix, flow and co-culture. The transcriptional profile of PTECs grown on a non-coated surface presented an enrichment of inflammatory markers such as TNF-a, IL6 and CXCL6, resembling that of diseased tubular biopsies. This inflammatory effect was not seen in PTECs grown on a matrix, and the growth conditions of matrix under flow further resembled the transcriptional profile of healthy tubular biopsies. Unsurprisingly, the presence of flow modulated the expression of kidney signature genes including drug solute transporters. Likewise, HGECs' transcriptional profile more closely resembled the profile of in vivo glomerular cells when grown on a matrix under flow.

Conclusions: In conclusion, PTECs and HGECS grown under different culture conditions present considerable transcriptional profile changes; being enriched in inflammatory pathways when grown on a non-coated surface, but closely resembling in vivo homeostatic profiles when grown with matrix and/or flow. These findings guide future selection of translatable models investigating renal physiology and pharmacology.

Funding: Commercial Support - AstraZeneca

Recreating Renal Function in a Human Glomerulus and Proximal Tubule Microphysiological System

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Background: Preclinical tests for pharmaceutical discovery extensively rely on static, 2D cultures and animal models. While these methods are commonly used, they poorly represent human responses due to the lack of architecture and physiological stimuli (2D culture), and human cells (animal models). Kidney microphysiological systems (MPS) better support renal function with controlled, 3D fluidic platforms, and serve as valuable tools in determining renal toxicity to new drugs. Current kidney MPS model proximal tubule (PT), there are currently limited options in terms of human cell types, scalable platforms for evaluation of drug toxicity, and tissue engineered solutions where the complexity of the PT is accurately modeled.

Methods: The MPS consisted of: T-Junction, glomerulus housing (GH), and PCT chip. Media from the bloodstream flowed into the T-Junction, splitting 10% of flow to GH. Fluidic channels for 5 days under physiological fluid shear (0.07 Pa) to establish confluent layers. Subsequently, a portion of the tissue replicates underwent simulated IR consisting of 3 days of static conditions followed by 2 days of physiological flow. Transepithelial electrical resistance (TEER) was measured daily, and all tissues were fixed after 10 days in culture for structural characterization via immunofluorescence confocal microscopy.

Results: TEER measurements highlighted a transient increase in barrier function (cultures control tissues) in response to the onset of ischemia, followed by a reduction in integrity over subsequent days that persisted through reperfusion. IR tissues exhibited primary cilia that were on average less abundant but roughly double the length of those exhibited by control tissues. This is consistent with previous observations of cilia lengthening among IR-injured kidney epithelia in vivo. IR tissues also displayed nuclear staining for β-catenin suggestive of a proliferative response to injury.

Conclusions: The described model has significant potential to clarify mechanisms of IR injury in the kidney.

Funding: Other U.S. Government Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underlines represent presenting author.
Niacin Supplementation Increases In Vitro Apicobasal Volume Transport and Oxygen Consumption by Proximal Tubule Cells

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Background: Renal tubule cells are energetically demanding as they consume ATP to transport salt and water within the kidney. In vitro, renal tubule cells have an attenuated glycolytic phenotype described as cell culture stress. We hypothesized that Krebs cycle intermediates may be rate-limiting in tubule cell function. The significant increase in acidification rates (ECAR) were assessed using a Seahorse XFe96 analyzer. Respiratory oxygen consumption.

Methods: Primary human renal tubule epithelial cells (iRECs) were seeded on polystyrene tissue culture plates and cultured with normal (2 mg/L) or high niacin (4mg/L). After two weeks of treatment, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFp96 analyzer. Respiratory inhibitors oligomycin (2µM), CCCP (2µM), rotenone (0.5µM), antimycin A (0.5µM) and 2-deoxyglucose (2-DG, 50mM), and glucose (10mM) were used to probe mitochondrial and non-mitochondrial respiration. Statistical differences between control and experimental groups were estimated by two-tailed Student’s t-test. Results are considered significant at p<0.05. Cells from the same lot were seeded on permeable supports and cultured with an inhibitor of TGF-b receptor 1 and low or high niacin concentrations.

Results: High-dose niacin was associated with increased oxygen consumption compared with normal dose niacin (225 vs 157 uMol/min, p < 0.01), and with increased transport (187 +/- 83 vs 87 +/- 2.8 uL/cm2/day; p < 0.0004).

Conclusions: Our observation that mitochondrial oxygen consumption increased with addition of supplemental niacin supports the hypothesis that Krebs cycle intermediates may be rate-limiting in tubule cell function. The significant increase in apicobasal transport with added niacin suggest that some of the dysfunctional phenotype induced by cell culture stress may be mitigated by nutritional supplementation.

Funding: Private Foundation Support

PO0497

Microenvironmental Influences on 3D Embedded and Bioprinted Induced Renal Tubular Epithelial Cells (iRECs)

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Background: Conventional cellular models of renal tubular origin only partially maintain their functional properties. Recent advances in 3D culture techniques and bioprinting technology promise to improve physiological conditions by reconstituting the tissue architecture in vitro. We previously described that direct reprogramming with a defined lentiviral cocktail of four transcription factors (Hnf1b, Hnf4a, Pax8, Emx2) can convert fibroblasts to induced renal tubular epithelial cells (iRECs). We analyzed how the microenvironment influences behavior, expression profile and the cellular function of iRECs to determine their utility for bioprinting applications.

Methods: iRECs were subjected to manual pipetting and inkjet bioprinting methods, embedded in three ECM-like microenvironments (Matrigel, Fibrin and Collagen I), and two culture media (DMEM and REGM). Morphology and viability of multicellular structures were assessed at several time points after seeding. Moreover, RNA-Seq was carried out to describe differentially regulated genes, and their protein products analyzed via immunofluorescence.

Results: iRECs showed high viability and biocompatibility with dispensing methods and bioinks. However, the morphology of multicellular aggregates was dramatically influenced by the microenvironment (e.g. they formed smaller spherical aggregates in Matrigel, but elongated tubule-like structures in Collagen I). Transcriptomic analysis revealed differentially expressed signature genes in each of the used biomaterials. For example, expression of apical endocytic machinery components was elevated in Matrigel embedded cells. In contrast, transcripts of ECM components showed strongest expression in the Fibrin condition. In addition, the tubule segment identity of iRECs was altered by the microenvironment. Microdispensing (drop on demand) bioprinting achieved perfusable tubule-like structures.

Conclusions: The design of specific tubule microenvironments for reprogrammed kidney tubule cells can be tailored to better reflect physiological conditions and to the desired purpose of vitro applications. This will facilitate the use of appropriate biomaterials to optimize the construction of biomimetic kidney tubule models at scale.

Funding: Government Support - Non-U.S.
Tunable Stiffness Amino Functionalized Polyacrylamide-Based Hydrogels for Renal Cell Tissue Culture

**Methods:** APMA was substituted in varying amounts in PA mixes previously reported to produce gels with expected stiffnesses of 2.6 kPa or 40 kPa. Gels were produced by free radical polymerization under nitrogen, using TEMED (1:300) and 10% ammonium persulfate (1:100). Gels were cast on glass coverslips soaked overnight in 2M NaOH, dried and treated with a 5% solution of 3-aminopropyltrimethoxy silane in isopropanol, then 1% glutaraldehyde. Gels were sterilized with 70% ethanol for 30 minutes, and then placed in sterile PBS. Different amounts of APMA were tested using primary human renal tubule cells (Lonza). The elastic modulus of the modified gels was measured using an Electroforce 3100 mechanical analyzer.

**Results:** Cells attached rapidly to gels in standard medium with 10-20% APMA substitution at both stiffness levels, and maintained excellent attachment for at least 6 weeks, under both static and shacking conditions. Cells proliferated on gels until confluent. Higher APMA amounts were less effective with softer gels. Cells initially attached to 5% APMA gels, but detached after 2-3 days. The addition of APMA decreased the stiffness of the softer gels by ~25%, while it increased by ~25% for the harder gels.

**Conclusions:** Primary human renal tubule cells were found to attach rapidly and remain on polyacrylamide hydrogels containing 10-20% APMA. Cells proliferated well on APMA-based gels, and remained attached for at least 6 weeks, even under fluid shear stress (~2 dyn/cm^2). We conclude that the addition of APMA to PA gels provides a very simple and reproducible method of functionalizing PA gels for renal cell attachment, and allows for the testing of soft, tissue-like substrates under physiological fluid flow conditions.

**Funding:** Private Foundation Support

PO0500

**Canonical TGF-β Signaling Mediates Renal Tubule Epithelial Cell Differentiation In Vitro**

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**Background:** Transforming growth factor-β (TGFβ) initiates multiple signaling pathways involved in the regulation of epithelial cell fate and cell plasticity. Here we identify canonical TGFβ signaling as a critical regulator of renal tubule epithelial cell membrane transporter expression in vitro.

**Methods:** Primary human renal tubule epithelial cells (HREC) were cultured on permeable supports on an orbital shaker. After two weeks in culture, cells were supplemented with TGFβ receptor I (TβRI) inhibitors SB431542 or A8301, Smad3 inhibitor SIS3, PI3K inhibitor LY294002, Rapamycin, p38 MAPK inhibitor SB203580, Takinib (2nM), Trametinib. After four weeks, apicobasal fluid transport and gene expression by RT-PCR was measured. Statistical differences were estimated by two-tailed Student’s t-test in MatLab.

**Results:** Canonical TGFβ inhibitors SB431542 and A8301 increase apicobasal fluid transport, while Smad3 inhibitor SIS3 does not. Non-canonical TGFβ inhibitors LY294002, Rapamycin, SB203580, Takinib, Trametinib do not increase apicobasal fluid transport. SB431542 and A8301 suppress Snail1 transcription, while SIS3 does not. SB431542 and A8301 increase AQP2 transcription, while SIS3 does not, and allows for a greater effect on NHE3 transcription.

**Conclusions:** Increased inhibitable transport by renal tubule cells in vitro appears to be mediated by canonical TGFβ signaling. The lack of response to SIS3 suggests that Smad2, rather than Smad3, is responsible.

**Funding:** Private Foundation Support

PO0499

**Tunable Stiffness Amino Functionalized Polyacrylamide-Based Hydrogels for Renal Cell Tissue Culture**

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**Background:** Tunable stiffness polyacrylamide (PA) based hydrogels have been utilized for tissue engineering studies. PA gels require functionalization for cell attachment. Reagents such as sulfo-SANPAH or acrylic acid NHS ester are often used to attach protein to the gel surface. However, these methods do not provide adequate binding to maintain cell attachment for studies involving fluid shear stress or long-term culture. In order to produce PA gels with uniform surfaces and robust cell attachment, we tested gels incorporating N-(3-Aminopropyl) methacrylamide (APMA) to create a positively charged polyelectrolyte-like biocompatible surface.

**Methods:** APMA was substituted in varying amounts in PA mixes previously reported to produce gels with expected stiffnesses of 2.6 kPa or 40 kPa. Gels were produced by free radical polymerization under nitrogen, using TEMED (1:300) and 10% ammonium persulfate (1:100). Gels were cast on glass coverslips soaked overnight in 2M NaOH, dried and treated with a 5% solution of 3-aminopropyltrimethoxy silane in isopropanol, then 1% glutaraldehyde. Gels were sterilized with 70% ethanol for 30 minutes, and then placed in sterile PBS. Different amounts of APMA were tested using primary human renal tubule cells (Lonza). The elastic modulus of the modified gels was measured using an Electroforce 3100 mechanical analyzer.

**Results:** Cells attached rapidly to gels in standard medium with 10-20% APMA substitution at both stiffness levels, and maintained excellent attachment for at least 6 weeks, under both static and shacking conditions. Cells proliferated on gels until confluent. Higher APMA amounts were less effective with softer gels. Cells initially attached to 5% APMA gels, but detached after 2-3 days. The addition of APMA decreased the stiffness of the softer gels by ~25%, while it increased by ~25% for the harder gels.

**Conclusions:** Primary human renal tubule cells were found to attach rapidly and remain on polyacrylamide hydrogels containing 10-20% APMA. Cells proliferated well on APMA-based gels, and remained attached for at least 6 weeks, even under fluid shear stress (~2 dyn/cm^2). We conclude that the addition of APMA to PA gels provides a very simple and reproducible method of functionalizing PA gels for renal cell attachment, and allows for the testing of soft, tissue-like substrates under physiological fluid flow conditions.

**Funding:** Private Foundation Support
PO0501

TGF-β Mediates In Vitro Renal Tubule Cell Fatty Acid Oxidation
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Background: Renal tubule cells (HREC) are energetically demanding due to their role in transporting solutes, and undergo a shift toward glycoplysis and away from oxidative phosphorylation of fatty acids in vitro. We identified Transforming Growth Factor-β (TGFβ) as a critical modulator of HREC differentiation. Here, we find that TGFβ inhibition increases HREC fatty acid oxidation.

Methods: Primary HREC were seeded on polycarbonate Transwells or polystyrene Seahorse XFe96 tissue culture plates. Cells were supplemented with AMPK activator metformin, TGFβ1 receptor I inhibitor SB431542, or a combination of both. After four weeks, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFe96. Glutamine oxidation inhibitor BPTES, fatty acid oxidation inhibitor etomoxir, and glucose oxidation inhibitor UK5099 were used to probe HREC substrate utilization. Gene expression was measured using RT-PCR. Statistical differences were estimated by two-tailed Student’s t-test. Results are considered significant at p<0.05.

Results: MET and SB43 stimulate transcription of electron transport chain Complexes I, II, IV, and V. Control and MET OCR did not respond to inhibitors. MET cells have diminished basal OCR and decreased ECAR in response to UK5099. SB43 increases basal OCR and cellular responses to UK5099 and etomoxir, implying increased glucose and fatty acid oxidation. SB43 increases transcription of fatty acid transporter CD36 and fatty acid oxidation genes FABP1, PPARα, and CPT2.

Conclusions: Inhibition of TGFβ increases in vitro transcription of mitochondrial and oxidative phosphorylation of fatty acids by HREC.

Funding: Private Foundation Support

PO0502

Investigating the Use of Smartwatch-Based Self-Assessments to Monitor Fluid Consumption of Hemodialysis Patients
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Background: Fluid intake control is a bedrock component of treatment for End Stage Kidney (ESKD) Patients, but continues to be a major challenge for patients, healthcare providers, and organizations. The ramifications of poor fluid control include increased mortality and morbidities, frequent hospitalizations and increased total cost of care. The goal of this work is to investigate the feasibility of leveraging self-assessments based on smartwatches to monitor fluid consumption of ESKD patients.

Methods: ESKD patients on hemodialysis (n=11) were given an Android smartwatch with an in-house developed app pre-installed (FitSense, available on Android play store). Patients were asked to log their fluid intake through the app by choosing from a list of predefined volumes each time they consume any liquid. The app computed and displayed their recorded daily volume intake to help patients monitor their own fluid consumption (Figure 1-A). Patients received text messages twice a day (9am and 8pm) to remind them to use the watch. We also recorded patients’ weights before and after each of the three weekly dialysis sessions. The sum of self-reported interdialytic fluid intake was computed and compared against the interdialytic weight gain recorded in the clinic.

Results: Patients recorded fluids in 214 days out of 259 total days (i.e., 83% compliance rate). The average self-reported interdialytic fluid consumption is 51 oz +/- 64, and the average interdialytic weight gain is 2.67 kg +/- 1.56. We found a moderate but significant correlation between the self-reported fluid volumes and the interdialytic weight gain (r=0.363, P<0.001, r^2=0.06).

Conclusions: Leveraging smartwatches for the self-assessment of fluid intake is a promising solution for fluid monitoring of ESKD patients. This can be related to the ease of utilization of this technology and the ecological validity of its measurements given they are collected close to when they happen, reducing recall biases. In the future, we will leverage low-burden sensor data to monitor patients’ fluid intake continuously and unobtrusively.

PO0503

Heterogeneous Local Hemodynamics in Rat Arteriovenous Fistula with Sildenafil Treatment
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Background: Arteriovenous fistula (AVF) maturation failure is an unmet clinical need. Alkant blood flow is thought to impair AVF remodeling, but previous literature has largely focused on hemodynamics averaged over the entire AVF. We hypothesize that hemodynamics is not uniform and thus any treatment’s effect size is not uniform in AVF. We used the PDE5A inhibitor sildenafil and performed MRI-based computational fluid dynamics (CFD) to test our hypotheses.

Methods: Femoral AVFs were created in young male Sprague-Dawley rats. Sildenafil was given daily starting at 14 days before AVF creation and continuing for 21 days, at which time rats underwent MRI. MRI scans were used for measuring cross-sectional lumen area (CSA), and for CFD to derived flow rate, wall shear stress (WSS), oscillatory shear index (OSI), and vorticity. Results were split into 4 zones: 0-5, 5-10, 10-15, and 15-20mm away from the anastomosis.

Results: Sildenafil treated rats had significantly larger CSA, flow rate, WSS, OSI and vorticity than control rats in all zones (p<0.05) (Fig. 1). In both groups: (1) While flow rate remains constant in all zones, CSA increased from 0-5 to 15-20 zone. (2) Velocity, WSS and vorticity were the highest in the 0-5 zone, and each parameter drops significantly thereafter. (3) OSI increases at the 5-10 zone and then decreases gradually.

Conclusions: Sildenafil increased CSA and hemodynamics parameters in AVF. The magnitudes of increases are heterogeneous along the AVF. Thus, the effect size of sildenafil on AVF remodeling and the association between hemodynamics and AVF remodeling depends on location. Increased knowledge of local hemodynamics and effect size may lead to treatments to improve AVF maturation.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

196
Effects of Smoothing Methods on Hemodynamic Assessment of a Human Arteriovenous Graft

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Background: Aberrant hemodynamics contribute to the formation of neointimal hyperplasia in arteriovenous grafts (AVG) for hemodialysis, but the detailed hemodynamic environment in an AVG is unclear. Computational fluid dynamics (CFD), while a useful tool for hemodynamic analysis, is influenced by lumen geometry. 3D vascular lumens reconstructed from medical images must be smoothed to remove surface deformities and improve their uniformity before being used in CFD. We investigated whether different smoothing methods may cause different hemodynamic analysis results.

Methods: MRI scans were performed on a dialysis patient’s AVG and then used to reconstruct a 3D AVG lumen, on which four smoothing methods were applied that vary in their uses of interpolation, unconstrained smoothing, and additional surface smoothing (Fig 1A, B). The four smoothed lumens were used in the same CFD protocol to calculate velocity, wall shear stress (WSS), and oscillatory shear index (OSI). Results from different methods were compared using standard deviation (SD) and relative standard deviation (RSD = SD/mean x 100%) (Fig 1C).

Results: All methods give similar AVG lumen areas (RSD<3%). Although velocity has RSDs of 6-9%, their SDs are <0.1 m/s, and thus the differences are not considered biologically significant. Along the same line, all methods do not give biologically significant differences in OSI, as the SDs are <0.01. However, different smoothing methods give very different WSS, with RSD >12% and large SDs.

Conclusions: A variety of smoothing methods can be used to create AVG lumen reconstructions for CFD and hemodynamic analysis. These different methods can lead to significantly different WSS values. Therefore, researchers should consider the smoothing techniques used to characterize the hemodynamic environment in an AVG.

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

Transdermal Glomerular Filtration Rate Measurement in Conscious Pigs Using the Novel Fluorescent Tracer Agent Relmapirazin

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Background: Transdermal measurement of glomerular filtration rate (GFR) using a miniaturized fluorescence detector (“TGRAF Mini Monitors”) in combination with a fluorescent exogenous GFR tracer agent is a common technique to measure kidney function in the preclinical setting, most commonly employed with rodents. However, larger animals are used in translational research on the way to human applications. The employ of an exogenous tracer agent in the preclinical setting which will also be amenable for seamless transition to human use would enhance the applicability of the preclinical data to clinical data.

Methods: The renal function of three healthy pigs (35-40 kg) was measured for 5 consecutive days. The novel fluorescent exogenous tracer agent Lumitrace™ (relmapirazin) was used in combination with two TGRAF Mini Monitors per animal (MediBeacon, Germany). Excretion kinetics were measured transdermally, as well as in plasma, over the course of 4 hours. After attachment of the devices on the animal’s skin, relmapirazin was administered intravenously. Seventeen blood samples were collected to measure plasma pharmacokinetics.

Results: The slopes of the single-exponential decay of the plasma kinetics and the transdermal kinetics of relmapirazin are in agreement (Slope 0.97; R²=0.57). No statistical differences were detected using a paired t-test.

Conclusions: The collected data supports the suitability of the TGRAF Mini Monitor to measure relmapirazin excretion kinetics in pigs, thus providing an important tool for translational research of GFR in larger animals.
PO0506
Modeling Rare Human Tuberous Sclerosis Complex-Associated Kidney Angiomyolipomas In Vivo with Induced Pluripotent Stem Cell-Derived Renal Organoid Xenografts
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Background: Currently there are no animal models of renal angiomyolipoma (AML) for the study of tumor mechanisms in vivo. This is partly due to the fact that biallelic inactivation of TSC1 or TSC2 during development causes embryonic lethality, while previous attempts to ablute TSC1 or TSC2 by means of tissue-specific Cre-mediated recombination have not succeeded in recapitulating the lesions.

Methods: We induced neoplastic differentiation of isogenic TSC2−/−, TSC2−/−, and TSC2−/− human iPSCs derived from a TSC patient, under three-dimensional tissue culture conditions for 21 days. Next we transplanted the resulting renal organoids under the kidney capsule of immunodeficient RNU nude rats. We next tested a novel formulation for ablation.

Results: The red line indicates the linear regression forced through the origin. Blue circles indicate the reciprocal RTDC derived from the transcutaneous and plasma measurement. The average baseline [Ca²⁺]i was observed when tubules were subject to luminal filling, sufficient to cause circumferential stretch and turbulent flow, resulting values of 36 to 272 ± 13 nM in organoids at 40 and 57 d of culture, respectively (n=3, p<0.002 vs. baseline). Luminal flow-induced increases in [Ca²⁺]i were not detected in tubules isolated from organoids <40 d in culture (n=3). Mechanosensitive Piezo1 channels contribute to the flow-induced [Ca²⁺]i response in the fully differentiated distal tubule (Carrizoza-Guyan et al., EB 2019). Nonperfused tubules exposed to bosutanol (PI3K/PI4K inhibitor) 100 nM (24-31 d in culture; n=4, p<0.0001) and from 130±36 to 504±197 nM (43-67 d in culture; n=4, p=0.002).

Conclusions: These preliminary results are consistent with a mechanotransduction in flow/stretch-sensitive Ca²⁺ channels, including Piezo1, and/or associated signaling pathways, in tubules of static organoid cultures.

Funding: NIDDK Support, Other NIH Support - R56 DK122380, UC2 DK 126023

PO0507
Functional Maturation of Kidney Organoid Tubules: Mechanosensitive Ca²⁺ Signaling
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Background: When grown under static conditions, kidney organoids derived from human pluripotent stem cells exhibit glomerular- and tubular-like structures. However, development is limited (Homan et al., 2019; Takasato et al., 2015). As the technology for culturing organoids advances, simulating tissue and drug interactions, the need to better characterize their physiological function has become a priority. To begin to functionally phenotype static organoids, we focused on characterizing mechanoo-induced changes in intracellular Ca²⁺ concentration ([Ca²⁺]i) signaling pathways in tubules isolated from maturing static organoids.

Methods: Tubular structures, microdissected from organoids between 21-57 d of culture, were microperfused in vitro or affixed to the base of a specimen chamber, and loaded with Fura-2-AM (20 nM) to measure [Ca²⁺]i. Digital ratio imaging was employed to individually identified cells by epifluorescence microscopy using commercial software.

Results: The average baseline [Ca²⁺]i in microperfused tubules was 180±13 nM (n=6). A rapid increase in [Ca²⁺]i was observed when tubules were subject to luminal filling, sufficient to cause circumferential stretch and turbulent flow, resulting values of 36 to 504 ± 36 nM in organoids at 40 and 57 d of culture, respectively (n=3, p<0.002 vs. baseline). Luminal flow-induced increases in [Ca²⁺]i were not detected in tubules isolated from organoids <40 d in culture (n=3). Mechanosensitive Piezo1 channels contribute to the flow-induced [Ca²⁺]i response in the fully differentiated distal tubule (Carrizoza-Guyan et al., EB 2019). Nonperfused tubules exposed to bosutanol (PI3K/PI4K inhibitor) 100 nM (24-31 d in culture; n=4, p<0.0001) and from 130±36 to 504±197 nM (43-67 d in culture; n=4, p=0.002).

Conclusions: These preliminary results are consistent with a mechanotransduction in flow/stretch-sensitive Ca²⁺ channels, including Piezo1, and/or associated signaling pathways, in tubules of static organoid cultures.

Funding: NIDDK Support, Other NIH Support - R56 DK122380, UC2 DK 126023
To demonstrate utility, the proposed NF-tubuloid platform was applied to screen the nephrotoxicity of 10 representative anti-cancer drugs.

**Results:** Specificity of KIM-1 NF sensors were demonstrated by studying a cell line constitutively expressing KIM-1 mRNA and adenosine-transfected tubuloids. NF ability to thoroughly label kidney tubuloids and report tubular injury were evaluated by applying several concentrations of aristolochic acid and cisplatin, two well-known nephrotoxins. Compared against its respective mRNA expression from qPCR, quantitated NF fluorescence showed a positive linear correlation with R^2=0.931, indicating its accurate representation of tubuloid status. Finally, the platform was used to facilitate nephrotoxicity screening of anti-cancer drugs, with significant tubuloid KIM-1 upregulation induced by 5-fluorouracil and paclitaxel.

**Conclusions:** We demonstrated the utilization of NF nanosensors to monitor injury on human kidney tubuloids. This platform enables facile and personalized nephrotoxicity assessment in vitro.

**Funding:** NIDDK Support, Other NIH Support - NCATS, Government Support - Non-U.S.

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**PO0510**

**Physiological Replication of the Glomerulus Using a Triple Culture Microphysiological System**

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**Background:** The glomerulus is a complex structure highly adapted for its function. A true representation of this in vivo cell-cell/ECM interactions, which provide the semi-permeable filtration barrier, is essential to interrogate physiological and pathophysiological processes and for understanding the impact of novel therapies.

**Methods:** We have developed a human microphysiological system with high fidelity to glomerular physiology and structure. For the first time the three resident cell types (glomerular epithelial cells (GECs), podocytes and mesangial cells (MCs)) reside in a relevant 3D structure under flow conditions. Analysis was performed on the individual cell types using both transcriptomics (NGS) and high content imaging to shed light on the impact of each cell type on its neighbors. Inulin and albumin permeability assays (fluorescent) were performed to evaluate the integrity of the glomerular barrier.

**Results:** Transcriptomic analyses demonstrated crosstalk between cells in our microfluidic tri-culture system. An influence of MCs was observed on both podocytes and GECs. For GECs, MCs increased tight junction proteins (CLDN7) and for podocytes there was a reduction of cell cycle control (MDM2). The differentiation of podocytes in the chip was able to regulate matrix and cell adhesion in MC (COL6A3, ITGA2) and influence angiogenic signals in GEC (KDR, THBS1). Analysis of pathways expressed in cells in the less complex comparison showed that they displayed transcriptomic signals akin to human disease phenotypes (comparison with signatures found in Nephroseq). Imaging showed increases in maturation markers such as synaptopodin in podocytes in triculture. Permeability assays revealed that as cell maturity increased barrier function improved and the passage of molecules was selectively hindered.

**Conclusions:** Our tri-culture model provides a highly physiologically relevant tool to study healthy glomerular function. This will enable improved understanding of the mechanisms underlying glomerulopathies and improved qualification of new therapies.

**Funding:** Commercial Support - AstraZeneca

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**PO0511**

**Biomimetic Platform for Quantitative Drug Screening of Podocyte Cytoskeletal Dynamics and Morphology**

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**Background:** Foot process effacement is driven by dysregulation of cytoskeletal dynamics. Currently, there are no drugs that primarily target the podocyte cytoskeleton due to dearth of in vitro model systems. To address this limitation, we designed a 3D drug discovery platform with a morpho-mimetic milieu that allows high-throughput quantitative measurements of drug-induced cytoskeletal changes in podocytes.

**Methods:** Immortalized human podocytes were differentiated on micropatterned surfaces fabricated via photolithography. High-resolution microscopy including confocal, TIRF, SEM and atomic force microscopy (AFM) were used to characterize morphometric and biomechanical properties. Protein expression was quantified using automated immunofluorescence, cell proliferation via EdU, and basal motility via fluorescent live-cell imaging. High-throughput analytical capabilities of the system were tested with cytoskeletal dose response against puromycin aminonucleoside (PAN).

**Results:** Cells cultured in 3D micropatterns for up to 14 days show a significant reduction in morphometric variability compared to unpatterned controls. During differentiation, micropatterned podocytes achieve cell cycle arrest faster and more robustly with reduced motility. Furthermore, the increased speed and the extent of cell cycle arrest is also observed in low serum, suggesting that the effects of morpho-mimetic culture are independent from biochemical stimuli. AFM elastography shows primarily a peripheral distribution of stiff actin fibers in micropatterned podocytes, mimicking in situ conditions. A cohesive cytoskeletal dose response was observed against PAN in the micropatterned cells only.

**Conclusions:** 3D micropatterns increase the speed and efficiency of podocyte differentiation while reducing cell-to-cell variability by up to 5-fold. Through its increased reproducibility, our automated system allows for quantitative in vitro study of podocyte morphology, cytoskeleton and biomechanics in response to drugs and pathogens with high fidelity and reproducibility.

**Funding:** NIDDK Support, Other U.S. Government Support

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**PO0512**

**Monitoring Mitochondrial Dynamics Within a Kidney-on-Chip Platform for Investigating Disease Progression and Potential Therapeutics**

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**Background:** The kidneys rely on an abundant number of mitochondria to produce energy to drive key functions, such as fluid/electrolyte balance. Mitochondrial dysfunction has been linked to the progression of renal diseases including acute kidney injury and diabetic nephropathy. Thus, the mitochondria are a key target for therapeutic development. Kidney-on-chip platforms provide a dynamic in vitro-like tissue culture environment to investigate renal pathophysiology. Yet, it is difficult or impossible to investigate mitochondrial dynamics due to lack of real-time measurements. Here, we present a sensor integrated kidney-on-chip platform with real-time cell oxygen consumption rate (OCR) readouts for monitoring the dynamics of mitochondrial function.

**Methods:** Human primary renal proximal tubule epithelial cells (hRPTEC) were cultured in PREDICT96 (P96), a high-throughput organ-on-chip platform. Integrated optical-based oxygen sensors enabled measurement of dissolved oxygen. Flow was turned off to measure decreases in oxygen and compute OCR. hRPTEC were treated with mitochondrial inhibitors Oligomycin and Antimycin A and un-coupler FCCP. OCR was measured prior to and following the drug treatment.

**Results:** hRPTEC basal OCR was monitored under flow at 70 uL/min over a 10 day culture period. OCR decreased by 58% and 39% following treatment with Antimycin A and Oligomycin, respectively, and increased 64% following treatment with FCCP (Fig.1).

**Conclusions:** We demonstrated real-time and label-free monitoring of drug-induced shifts in mitochondrial respiratory within a high-throughput kidney-on-chip platform. Our work enables new investigations into mitochondrial dynamics in response to nephrotoxic agents or disease progression, as well as potential therapeutics that target the mitochondrion.

**Funding:** Other U.S. Government Support

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**Figure 1:** OCR shifts during drug treatment. Bars are mean ± std (N=3-4 devices). **p<0.01, ***p<0.001, one-way ANOVA. **

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

*Underline represents presenting author.*
PO0513
Demonstrating Preclinical Proof of Concept of an Implantable Bioartificial Kidney (iBAK)

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Background: An implantable bioartificial kidney (iBAK) would provide continuous and convenient treatment while overcoming the challenges of dialysis and renal transplant. We previously demonstrated small-scale operational versions of an immunoprotective renal tubule cell-containing bioractor and a pumless hemofilter utilizing biomimetic silicon nanopore membranes (SNM). Here we report the successful integration of bioractor and hemofilter components into an iBAK prototype that demonstrated operational feasibility in swine.

Methods: Designs of the bioractor and hemofilter were optimized using computational fluid dynamics. Porcine renal (LL-CPK1) cells were cultured on collagen-coated Transwell® (Corning) membranes and inserted into the bioractor. A hemofilter containing SNM with ~10 nm-wide pores was connected to the bioractor in series through the hemofilter blood outlet and bioractor blood inlet. The iBAK was implanted into the retroperitoneum of a healthy Yucatan mini-pig, with anastomoses from the hemofilter blood inlet and bioractor blood outlet to the iliac artery and vein, respectively, and the bioractor ultrafiltrate outlet connected to the bladder. The pig did not receive systemic anticoagulation or immunosuppression. After 3 days, patency was assessed via angiogram and the device was explanted for further analysis. Cell viability was assayed using a LIVE/DEAD™ Cell Viability Assay (Invitrogen).

Results: The iBAK was successfully assembled and implanted with no procedural complications. Post-operatively the pig did not demonstrate signs of sepsis/hematoma, thromboembolism, infection, or other adverse reactions. 3 days after implant, the device was patent. Ultrafiltrate was noted at both implant and explant, with a flow rate of 0.28 mL/min measured at explant. Cells demonstrated ~80% viability, relative to in vitro controls. No gross thrombi or protein films were observed on the SNM.

Conclusions: We successfully integrated hemofilter and bioractor components to create a small-scale iBAK. The hemofilter generated ultrafiltrate from blood while the bioractor sustained renal cells and delivered ultrafiltrate (“urine”) to the bladder. This feasibility study will guide future development of a clinical-scale iBAK.

Funding: Other NIH Support - NIBIR Quantum Grant, Private Foundation Support

PO0514
A 20-Lb Portable Continuous Renal Replacement Therapy (PCRRT) Machine

Biosystems, Inc.

Background: CRRT is challenging due to needing large amounts of sterile fluids excessive labor and cost. Prescribed treatment is frequently interrupted when patients are transported out of the ICU for tests and procedures. Hence the unmet need for a light and portable bioractor operated CRRT machine that uses less fluids and nursing labor and can be used anytime at any place, including during procedures or transportation.

Methods: The machine connects to a central venous catheter and blood is heparinized and propelled through the blood compartment of a 0.6 sqm dialyzer and recirculated back to the central vein. 300 ml of sterile 0.45% is circulated into the dialysate compartment of the dialyzer. Calcium, magnesium, and sodium bicarbonate are added to the dialysate. Potassium and other additives may also be added. Blood and the dialysate are propelled by a double channel pulsatile pump. The volume of fluid removal is controlled by a volumetric separate pump. The spent dialysate coming out of the dialyzer is circulated by a double channel pulsatile pump. The volume of fluid removal is controlled by a

PO0515
High Sodium Reduced the Expression of PTH1R and Klotho by Inhibiting 1,25(OH)2D3 Synthesis

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Background: The proximal tubule epithelial (HK-2) cells were treatment with different concentrations of sodium/phosphorus. The expressions of 1α-OHase (Cyp27b1) and 24-OHase (Cyp24a1) were determined by RT-PCR and Western Blot respectively. LC/MS and ELISA was used to detect the levels of 1,25(OH)2D and intraacellular Ca2+; (Ca2+)i was detected with the Ca2+ indicator dye Fura-4. Chromatins samples were immunoprecipitated with antibodies against PTH1R and Klotho.

Results: High sodium decreased the expression of 1,25(OH)2D3 through reducing 1α-OHase and 24-OHase in HK-2 cells. Sodium phosphorus transporter inhibitor (PFA) and sodium hydrogen transporter inhibitor (Caliporide) increased the expression of 1α-OHase and 24-OHase, while ouabain decreased their expressions. High sodium intervention increased intracellular calcium concentration, but not calcium reversed high sodium induced 1α-OHase and 24-OHase expression. High sodium reduced the expression of PTH1R and klotho, combined use of PFA and Caliporide significantly increased the gene and protein expressions of PTH1R and klotho, while ouabain intervention further decreased their levels. Vitamin D receptor agonists significantly increased the recruitment of VDR to the VDRE of PTH1R and Klotho promoter, thus increased the expression of PTH1R and klotho.

Conclusions: High extracellular calcium can not only lead to a decrease in the synthesis of active vitamin D in the proximal tubules, but also affect the gene regulation of 1,25(OH)2D3. Intraacellular Ca2+; ([Ca2+]i) was detected with the Ca2+ indicator dye Fura-4. Chromatins samples were immunoprecipitated with antibodies against PTH1R and Klotho.

Forskolin, an adenylyl cyclase activator, was used as a positive control for cAMP production. All experiments were performed in triplicate.

Other U.S. Government Support, Commercial Support - Wearable Artificial Organs Inc
Bone and Mineral Metabolism: Causes and Consequences
Poster

PO0517
Bone Expression of Sclerostin in CKD and Dialysis Patients
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Background: Sclerostin, a 22-kDa glycoprotein secreted by osteocytes, negatively regulates bone formation through the inhibition of the Wnt/β-Catenin pathway. In patients with CKD, circulating sclerostin correlates negatively with bone formation but the impact on bone expression of sclerostin requires further investigation.

Methods: 87 pediatric patients with CKD underwent iliac crest bone biopsy with the quantification of sclerostin bone expression using immunohistochemistry (IHC). Subjects with circulating sclerostin values at the upper and lower extremes of each population (n=6 CKD and n=6 dialysis) underwent staining with two β-catenin antibodies that recognize the phosphorylated/unphosphorylated states.

Results: The median (IQR) age of the cohort was 17 (14, 20) and 39% had pre-dialysis CKD (Table). Significant correlations between IHC sclerostin and bone histomorphometry were limited to the dialysis group: IHC sclerostin correlated with bone formation rate (r=0.34, P=0.02) and osteoid thickness (r=0.3, P=0.03). In the sub-group undergoing β-catenin staining, dialysis patients demonstrated low bone staining of sclerostin independent of circulating sclerostin. CKD subjects with high circulating sclerostin levels (ranging from 88 to 110 pmol/L) demonstrated increased sclerostin staining in osteocytes when compared with CKD patients with lower serum sclerostin (ranging from 30 to 36 pmol/L). Phosphorylated β-catenin staining was higher and unphosphorylated β-catenin levels lower in bone tissues with high circulating sclerostin.

Conclusions: Together, these data support a model whereby high levels of circulating sclerostin from osteocytes contributes to altered bone remodeling through aberrant Wnt signaling activity in CKD and may provide a rationale to target therapeutic strategies using monoclonal antibodies towards sclerostin.

Funding: NIDDK Support

PO0518
The Essential Role of miRNA in Maintaining an Intact Parathyroid in the Adult
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Background: miRNA are small noncoding RNAs with vital roles in homeostasis and development. Dicer mediates the final step of miRNA maturation. To study the roles of miRNA in the parathyroid, we generated parathyroid specific Dicer knockout (PT-Dicer-/-) mice, to specifically delete parathyroid miRNA. The PT-Dicer-/- mice had normal serum PTH levels, but failed to increase PTH when stressed by hypocalcemia or kidney failure, unlike control mice and patients. We now show that in addition to parathyroid stimulation, miRNA are central to maintaining intact parathyroid glands throughout life.

Methods: We generated PT-Dicer-/- and control mice expressing YFP (Yellow Fluorescent Protein) in the parathyroid by cre lox recombination, to track parathyroid cells by fluorescence microscopy. Histological slides from P0 (day of birth) and older mice were immunostained. qRT-PCR and Western blots were performed on thyroid tissue that includes the embedded parathyroids.

Results: Surprisingly, adult PT-Dicer-/- mice had no YFP positive parathyroid glands detected by fluorescence microscopy, as opposed to easily detected intact glands in controls. However, the glands were present immediately after birth in P0 and P1 Dicer-/- mice. At P0 and P1, there were increased levels of the cleaved caspase-3 apoptotic marker in cells co-expressing PTH and the parathyroid transcription factor GCM2. From P3 to P12, there was a gradual loss of parathyroid glands in PT-Dicer-/- mice, with the left gland disappearing last. qRT-PCR of thyroid RNA, containing the parathyroid when present, showed reduced expression of PTH mRNA in adult PT-Dicer-/- mice, compared to controls. PTH levels were also decreased in thyroid extracts as determined by Western blots. There was no change in thymus PTH mRNA that has been proposed to provide an auxiliary source of PTH.

Conclusions: Mice that do not express miRNA in the parathyroid lose their parathyroid glands after birth, indicating that miRNA are not essential for parathyroid embryonic development by rather postnatally, for maintaining intact parathyroid glands. In the absence of parathyroid glands in adult PT-Dicer-/- mice, an additional source for PTH other than cells in the thyroid or thymus contributes to normal basal serum PTH that cannot be stimulated by hypocalcemia or uremia.

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201
Calcimimetics Alter Periosteal and Perilacunar Bone Matrix Properties in Early CKD

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Background: Chronic kidney disease (CKD) patients have an elevated fracture risk due to hyperparathyroidism, cortical porosity, and reduced bone material quality. Calcimimetic drugs are used to lower PTH in dialysis patients, but their impact on bone matrix quality in early CKD remains unknown. We hypothesized that tissue-level bone quality is altered in early CKD and that calcimimetic treatment improves bone quality.

Methods: Male C57/BL6 rats fed a casein-based diet underwent progressive CKD with mineral and bone disorder. 18-week-old rats (stage 3 CKD, N=12) were treated with the calcimimetic KP-2326 (0.6 mg/kg ip. 3x/wk). N=12 normal littermates (NL) and untreated CKD rats received the casein diet to control mineral intake. Calcein was administered 4 and 14 days prior to sacrifice at 28 weeks (stage 4 CKD). Blood was drawn and femora were harvested for MicroCT and 4-point bending. Femur sections were cut and polished for colocalized Raman spectroscopy and nanoindentation. Colocalization was run in fluid in periosteal bone using calcein as a guide and in concentric ellipses around osteocyte lacunae.

Results: PTH was 284% higher in CKD vs NL and KP reduced PTH by 92% vs CKD. Neither CKD nor KP altered cortical porosity and KP did not improve structural mechanical properties vs CKD. In new periosteal bone, CKD reduced carbonate substitution by 29% and elastic modulus by 15% vs NL while KP increased mineral crystallinity by 4% vs NL and restored elastic modulus to NL levels. In perilacunar bone, KP reduced carbonated substitution and increased elastic modulus and hardness vs CKD.

Conclusions: This study demonstrates that CKD and KP alter bone matrix composition via changes in carbonate properties on the tissue level prior to structural changes such as cortical porosity. The perilacunar data suggests that osteocytes may actively alter their surrounding matrix in CKD and that calcimimetics may help prevent these changes prior to a decline in bone structural integrity.

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Conclusions: We conclude that 2D intestinal organoid cultures are suitable in vitro models to study oxalate transport from mice and humans. Using these models we demonstrated that Slc26a6-mediated chloride-oxalate exchange protects from intracellular oxalate accumulation and cell death.

Funding: Government Support - Non-U.S.

PO0524
Optimization of Oxalobacter formigenes-Derived Small Peptides with Therapeutic Potential for Hyperoxalemia, Hyperoxaluria, and Related Kidney Stones
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Background: Most kidney stones (KS) are composed of calcium oxalate, and very small increases in urine oxalate enhance the stone risk. Besides KS, oxalate also potentially contributes to CKD progression and CKD - and ERSD-associated cardiovascular diseases, emphasizing the need for plasma and oxalate urinary lowering therapies, and enhancing the bowel’s ability to secrete oxalate may effectively do so. We previously discovered Oxalobacter-derived secreted factors stimulating oxalate transport by human intestinal Caco2-BBE (C2) cells and reducing urinary oxalate excretion in hyperoxaluric mice by inducing colonic oxalate secretion. We identified the small peptides P8 and P9 as the major secreted factors and they have significant therapeutic potential for hyperoxalemia and hyperoxaluria. Natural peptides are often not suitable therapies due to rapid degradation by proteolytic enzymes, and P8 & 9 peptides have multiple enzymatic cleavage sites.

Methods: Described under Results.

Results: To optimize P8 & 9 peptides and make them resistant to proteolytic degradation, there were subjected to the following structural modifications. N-terminal acetylation (P8-Ac & P9-Ac), C-terminal amidation (P8-Am & P9-Am), retrosubstitution (P8-RI & P9-RI), and replacing several glycine and lysine sites with PEG6 (P8-P & P9-P) & ornithine (P8-O & P9-O), respectively. All of these modified peptides stimulated oxalate transport by Caco2 cells similar to the native P8 & 9, except P8-RI (47.3% less functional) and P8-R1 (nonfunctional). The native and modified peptides were then treated with different enzymes (trypsin, proteinase K, and colonic lavage fluid [CLF: mimics the colonic environment]) to evaluate the impact of such modifications using LC-MS and/or HPLC as a qualitative and quantitative assay. Native and modified peptides (P8-9-Ac, P8-9-Am, & P8-9-P) were completely degraded by the above enzymes. P8-O and P9-O have improved stability (~75-80%) against trypsin, but were fully degraded by proteinase K and CLF. Importantly, P9-R1 is completely resistant to degradation by the above enzymes.

Conclusions: The current study shows that P8-R1 is the most stable modified peptide, but is less functional compared to native P9. Studies are ongoing to evaluate its in vivo therapeutic effects in lowering plasma and urinary oxalate levels in hyperoxalemia and hyperoxaluric mice.

Funding: NIDDK Support

PO0526
Transcriptomic Mapping of the Human Kidney Papilla Reveals Myeloid Activation and Matrix Remodeling Pathways in Stone Disease
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Background: The role of the kidney papilla in the pathophysiology of stone disease remains unclear. The aim of this study was to identify the cellular and molecular determinants of nephrolithiasis by molecular mapping of the stone forming papilla using integrated single nuclear and spatial transcriptomics.

Methods: Renal papillary biopsies were obtained from Calcium oxalate (CaOx) stone formers and reference non-stone formers. Tissue sections were prepared according to Visium (10x Genomics) spatial transcriptomic protocol. Single nucleus RNA sequencing from papillary frozen sections was used to spatially map the signature of specific cell types within the tissue. Data analysis and visualization were performed in R (seurat, ReactomePA, ClusterProfiler) and Loupe browser. In-situ RNA-seq of cell distribution and pathway activation were quantified using 3D immunofluorescence imaging. The levels of select proteins in urine samples were quantified by ELISA.

Results: Genes and pathways associated with reactive oxidative stress, myeloid immune activation and extracellular matrix (ECM) remodeling were significantly upregulated in CaOx biopsies relative to non-stone forming reference. Spatial transcriptomic localized the signature of specific cell types and demonstrated the increased expression of genes from those pathways such as FOS, JUN, SOD2, CCL2, TNF, and MMP2 & 9, particularly in areas within or adjacent to mineralized regions in the stone forming papilla. 3D immunofluorescence imaging confirmed the observed activated stress response and myeloid immune activation during phosho-c-JUN and CD68 staining, respectively. Additionally, the activation of myeloid and ECM remodeling pathways was validated by increased levels of MMP7 and MMP9 in the urine of patients with stone disease compared to healthy controls.

Conclusions: Using integrated transcriptomic and imaging approaches, we demonstrate that the papilla of stone patients is an active site of myeloid immune activation, reactive oxygen species and matrix remodeling. This immune active state has a molecular profile comparable to atherosclerotic disease. Our studies also uncover potential novel markers for screening and activity assessment of important pathogenic pathways in stone patients.

Funding: NIDDK Support

PO0527
Assessment of Vascular Calcification Using Micro-CT Quantification in a Vitamin D Rat Model
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Background: Micro-computed tomography (micro-CT) scanning could be an alternative technique of both visualization and quantification of calcium content in vessels. Our aim was to standardize the micro-ct calcium quantification methodology and evaluate its reliability in a rat model of calcification.

Methods: Six Sprague-Dawley rats were induced by three consecutively daily subcutaneous administrations of 150 µl/kg vitamin D3 and sacrificed 5 days after induction. Three of the rats were subcutaneously treated with 60 mg/kg SNF472 (G1), an inhibitor of calcification, and the rest were treated with saline (G2). One additional rat was not induced nor treated and served as negative control. Micro-CT was performed in aorta and femoral arteries with an isotropic resolution of 45 µm, 400 projections collected in one full rotation of the gantry in 10 min, x-ray tube at 80 kV and 150 µA. A phantom made of a laser cut aluminum skeleton was scanned with the same protocol to simulate bone. After the image analysis, the vessel samples were digested (1:1 HNO3/HClO4) and total calcium was quantified using an inductively coupled plasma atomic emission spectrometry (ICP-AES).

Results: The threshold for calcium detection was established at 153.8 Hounsfield Units (HU). Rats treated with vitamin D presented more calcium deposits than the control and SNF472 treated rats (7.6 ± 6.1 HU in G2 vs 3.3 ± 3.2 HU in G1). The volume of calcium deposits in femoral samples was similar between groups. The quantification of calcium by ICP-AES brought similar results in aorta (>50% inhibition with SNF472 induction). The calcium deposits in femoral samples was similar between groups. The quantification of calcium by ICP-AES brought similar results in aorta (>50% inhibition with SNF472 induction).

Conclusions: The threshold-based quantification method by micro-CT can be a useful and reliable tool to evaluate vascular calcification and the efficacy of inhibitors of vascular calcification in rat models, especially in large-diameter vessels such as aorta.

Funding: Commercial Support - Sanifit Therapeutics

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Poster
The Effect of the Warfarin-TG2-MVs Axis in Vascular Calcification

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Background: Warfarin is a common anti-coagulant drug. How to effectively reduce vascular calcification induced by warfarin while ensuring its anti-coagulant effect is an urgent problem to be solved. Previous studies have found that warfarin enhances the expression of osteogenic marker genes, namely bone morphogenic protein 2 (BMP2), in vascular smooth muscle cells (VSMCs), which mediates communication between cells and extracellular matrix (ECM). Matrix vesicles (MVs) are the center of hydroxyapatite crystal precipitation, which is released to ECM and interacts with ECM protein to initiate mineralization and form calcification core. This study observed the role of warfarin-TG2-MVs axis in vascular calcification by culturing VSMCs in vitro.

Methods: VSMCs were cultured in normal or osteogenic medium (OM) and stimulated with 10 µM warfarin for 3-14 days. The expressions of SM22α, Runx2, ALP, OPN, and TM were measured by reverse transcription polymerase chain reaction (RT-PCR). Alizarin red and von Kossa staining were performed to evaluate calcification, and calcium content was determined. Meanwhile, the expression and activity of TG2 were detected. Differential centrifugation was used to extract MVs and evaluate their release. Type I collagen was coated in the culture dish to determine the calcification of MV-collagen.

Results: Warfarin stimulation promoted transdifferentiation of VSMCs, that the expression of osteogenic factors Runx2, ALPL and OPN were increased, while the expression of SM22α and calcification inhibitor OPG were decreased. When using OM, the above trend was more obvious. Alizarin red and von Kossa staining were performed when the cells were cultured for 14 days. The results of calcium staining in the warfarin intervention group were all positive. Warfarin promoted the expression and activity of TG2, and it gradually increased with the extension of the intervention time. The same amount of MVs were cultured for 7 days under different stimuli, and the medium was exchanged every other day. Then, the supernatant was collected for differential centrifugation. The amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in type I collagen was increased.

Conclusions: Warfarin increased the expression and activity of TG2, promoted the release of MVs from VSMCs, and further cross-linked ECM to aggravate vascular calcification.

Uremic Milieu Exacerbates Muscle Regeneration After Muscular Injury in Mice

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Background: In our life, skeletal muscle injuries occur not only in strenuous exercises but also in daily activities with unexpected excessive muscle contraction. In general conditions, injured muscles are repaired to normal structure, and muscle functions are rescued. However, whether this repair process is affected in the uremic milieu has not been fully elucidated yet.

Methods: In C57BL6 male mice fed with normal diet or 0.2% adenine-conjugated diet, the muscle injury was induced by intramuscular injection with vehicle (PBS) or barium chloride (BaCl2) in tibialis anterior (TA) muscles. Then, we evaluated the TA muscle mass, weight, histology, muscle strength, and marker gene expressions of Pax7, satellite cells and macrophages playing a pivotal role in muscle regeneration. We also treated differentiating mouse skeletal myoblasts with a representative uremic toxin, indoxyl sulfate (IS), and evaluated the cell morphology and marker gene expressions.

Results: In adenine-induced CKD mice, the BaCl2-induced TA muscle showed reduction of muscle wet weight, muscle fiber size, instantaneous muscle strength, and Pax7 gene expression compared to control mice. Furthermore, the gene expression of DLL1 and Notch2 regulating the Pax7 expression, CCL5 accelerating the migration of macrophages, and cell surface markers of MU2 macrophages (CD206, CD163, and CD68) also increased in the injured muscle of CKD mice. Treatment of murine C2C12 myoblast with IS led to not only the myotube atrophy but also smaller number of nuclei per myotube. The gene expression of Pax7, DLL1, and CCL5 increased during the C2C12 myoblast differentiation, but IS treatment deteriorated these expressions as seen in vivo experiments.

Conclusions: Uremic milieu deteriorated muscle regeneration with the decline of gene expression associated with satellite cells and macrophages.

Indoxyl Sulfate Induces Cardiomyocyte Hypertrophy via FGF23-FGFR4 Signaling Pathway

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Background: Both fibroblast growth factor 23 (FGF23) and indoxyl sulfate (IS) have been reported to relate with left ventricular hypertrophy (LVH) in patients with chronic kidney disease (CKD), but their inter-relationship remains unknown.

Methods: To induce LVH, 8-week-old male C57BL/6J mice were fed high phosphorus diet after administration of transglutaminase 2 (TG2) in vascular smooth muscle cells (VSMCs), which mediates communication between cells and extracellular matrix (ECM). Matrix vesicles (MVs) are the center of hydroxyapatite crystal precipitation, which is released to ECM and interacts with ECM protein to initiate mineralization and form calcification core. This study observed the role of warfarin-TG2-MVs axis in vascular calcification by culturing VSMCs in vitro.

Results: IS promoted cardiac hypertrophy, and inhibition of FGF23 reduced heart weight and left ventricular wall thickness in IS groups (p < 0.05). There was no significant difference in serum FGF23 level among experimental groups, but the expressions of FGF23 protein and mRNA in the heart were markedly increased in IS-injected mice compared to control mice (p < 0.05). In cultured H9c2 cells incubated with IS, intact FGF23 protein level and phosphorylation of FGFR4 were increased, but intact FGF23 protein level in the medium didn’t change. The mRNA levels of β-miosin heavy chain (βMHC), o-smooth muscle actin (αSMA), brain natriuretic peptide (BNP), polypeptide N-acetylgalactosaminyltransferase 3 (Galnt3), and FGF23 were significantly up-regulated (p < 0.05), but collagen I was not.

Conclusions: IS increased intact FGF23 protein expression and activated FGF23-FGFR4 signaling in cardiomyocyte, leading to LVH, and FGF4R inhibition suppressed IS-induced LVH.

Hyperphosphatemia Contributes to Skeletal Muscle Atrophy in the Absence and Presence of CKD

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Background: Chronic Kidney Disease (CKD) is a public health epidemic and associated with elevated serum levels of phosphate (hyperphosphatemia) as well as skeletal muscle atrophy, and the interconnection is poorly understood. Elevated phosphate (Pi) has direct effects on smooth muscle cells and induces vascular calcification. We wanted to test if Pi directly induces atrophy in skeletal muscle cells. Furthermore, we analyzed skeletal muscle on a functional, histological and molecular level in three models of hyperphosphatemia – two CKD models, i.e. mice with global deletion of collagen 4α3 (Col4α3-/-) and wildtype mice receiving an adenine-rich (0.2%) diet for 14 weeks or a 0.3% Pi diet for 3 months. We analyzed strength, hindlimb area by MRI, muscle weight, cross-sectional area of individual muscle fibers immunolabeled with anti-laminin by fluorescence microscopy, and expression levels of atrogenes PiCR.

Results: Pi treatments increased the expression levels of atrogenes in C2C12 myoblasts. In the three mouse models, grip strength and cross-sectional area of myofibers were significantly reduced, and the expression levels of atrogenes were significantly elevated when compared to respective controls. Additionally, the two CKD models showed significant reductions in muscle weight and hindlimb area. Administration of a 0.2% Pi diet protected Col4α3-/- mice from developing skeletal muscle atrophy.

Conclusions: Elevated Pi induces myotube atrophy in vitro. Mice models with hyperphosphatemia develop skeletal muscle atrophy in the presence and absence of CKD, and a low Pi diet protects the skeletal muscle in CKD mice. Pharmacological approaches targeting Pi uptake or excretion, or inhibition of Pi’s direct actions on tissues might alleviate various CKD-associated pathologies.

The bone-derived hormone fibroblast growth factor (FGF) 23 targets the kidney to promote urinary phosphate (Pi) excretion by activating the FGF1/1Klotho/ERK1/2 signaling in renal proximal tubule (PT) cells. This reduces type II sodium phosphate co-transporters NaPi-2a and NaPi-2c in the apical brush border membrane (BBM) lowering serum Pi levels. In vitro data show that under high extracellular Pi, the target organ-dependent phosphate transporters NT1 and NT2 activate ERK1/2, and a low Pi diet protects the skeletal muscle in CKD mice. Pharmacological approaches targeting Pi uptake or excretion, or inhibition of Pi’s direct actions on tissues might alleviate various CKD-associated pathologies.

Methods: We subject C57BL/6N male mice to increased dietary Pi load (0.8% vs. 2%) for 6 months to determine phosphate homeostasis and analysing kidneys by qPCR.

Results: Phosphate levels were increased in the 2% Pi diet group compared to the 0.8% Pi diet group.

Conclusions: Phosphate levels were increased in the 2% Pi diet group compared to the 0.8% Pi diet group.

Renal FGF-23 Resistance by Phosphate Leads to NaPi-2a Internalization via Activated PI3K/IRK1/2 Signaling in Proximal Tubule

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Background: The bone-derived hormone fibroblast growth factor (FGF) 23 targets the kidney to promote urinary phosphate (Pi) excretion by activating the FGF1/1Klotho/ ERK1/2 signaling in renal proximal tubule (PT) cells. This reduces type II sodium phosphate co-transporters NaPi-2a and NaPi-2c in the apical brush border membrane (BBM) lowering serum Pi levels. In vitro data show that under high extracellular Pi, the target organ-dependent phosphate transporters NT1 and NT2 activate ERK1/2, and a low Pi diet protects the skeletal muscle in CKD mice. Moreover, Pi-regulated osseous FGF23 secretion is facilitated via PI3K. Here we aim to analyze Pi versus FGF23 regulated Pi transport in the setting of high phosphate load in renal PT cells.

Methods: We subject C57BL/6N male mice to increased dietary Pi load (0.8% vs. 2%) for 6 months to determine phosphate homeostasis and analysing kidneys by qPCR, immunoblot and histology. In addition, we study cultured renal PT cells treated with phosphate or FGF23 to examine the activation of downstream signaling events and

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expression levels of specific target genes. Furthermore, we determine if co-treatment with the cigarette smoke transporter inhibitor Foscarnet blocks the observed effects.

Results: A 2% Pi diet promotes the elevation of plasma FGF23 levels in mice. Despite reduced TRP, increased FGF23 and urine Pi levels, the serum Pi levels are still enhanced. In animals fed a 2% Pi diet, we observed reduced renal NaPi-2a mRNA expression and a reduced staining revealed of NaPi-2a from the apical BBM due to the high dietary Pi load. This is confirmed by analyzing BBM vesicles. Interestingly, mice on 2% Pi diet have a diminished renal Klotho expression, but unaltered Fgfr1 expression. Pi-T2 expression is increased and accumulated in the basolateral membrane of PT. In addition, the media was also quantified for Pi-T2 expression. The Pi-mediated increase in ERK1/2 phosphorylation was blocked by Foscarnet co-treatment.

Conclusions: Hyperphosphatemia might be a result of Pi-T2/ERK1/2-mediated downregulation of NaPi-2a stimulated by Pi itself. Our study indicates these Pi-mediated effects may be independent of FGF23. We postulate that high dietary Pi load causes a resistance of renal DMP1/Klotho signaling.

PO0533
Recurrent of Hypophosphatemia Despite FGF-23 Reduction in Dmp1 Knockout Mice
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Background: Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone produced by bone. Hyperphosphatemic rickets diseases, such as X-linked hypophosphatemia (XLH) and autosomal recessive hypophosphatemic rickets (ARHR), are characterized by elevated plasma phosphate, impaired skeletal growth and osteomalacia. Treatment with FGF23 blocking antibody has shown great promise to improve serum phosphate (Pi) levels and bone mineralization in XLH. Further studies need to determine if blocking FGF23 is efficacious in the long term and in other diseases associated with FGF23 excess, including ARHR.

Methods: We deleted Fgfg3 in osteocytes using a Dmp1-driven cre in wild-type (WT) and Dmp1 knockout (Dmp1KO) mice. We studied the bone and mineral phenotype of WT, Fgfg3 KO, Fgfg3 KO and Fgfg3 KO/Fgfg3 KO mice at 12 and 20 weeks of age.

Results: Fgfg3 KO mice showed a 40% reduction in serum intact FGF23 levels and a 25% increase in Pi levels (vs. WT), confirming successful deletion. As expected, DMP1 deficiency in Dmp1 KO mice induced significant elevations in serum FGF23 levels (+15 fold) and PTH levels (+5-fold), phosphaturia, hypophosphatemia, rickets and osteomalacia (vs. WT). At 12 and 20 weeks, osteocyte specific deletion of Fgfg3 in Dmp1 KO mice partially corrected FGF23 levels (+80%), PTH levels (-50%), and ameliorated the bone phenotype (+50% in femur length and bone mineral density) (vs. Dmp1 KO). Partial reduction of FGF23 levels was sufficient to correct serum Pi levels in 12 week-old (NS vs WT) but not in 20 week-old Dmp1 KO/Fgfg3 KO mice which showed recurrent hypophosphatemia despite nearly normal FGF23 levels. In contrast, phosphaturia persisted in Dmp1 KO/Fgfg3 KO mice at 12 and 20 weeks (vs. Dmp1 KO), suggesting that lowering FGF23 and PTH is insufficient to prevent phosphaturia in Dmp1 KO mice.

Conclusions: These data suggest that in Dmp1 KO mice, hypophosphatemia is only partially responsible for the bone defects and that blocking FGF23 may not be sufficient to prevent hypophosphatemia in the long term.

Funding: NIDDK Support

PO0534
Linking CKD with COPD: Kidney-Lung Cross-Talk and the Role of Phosphate and FGF-23 in the Bronchial Epithelium
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Background: Dysregulation of phosphate homeostasis and increased circulating FGF23 levels are associated with chronic kidney disease (CKD); however, their role in pulmonary pathology remains poorly defined. Hyperphosphatemia is associated with increased mortality in patients with chronic obstructive pulmonary disease (COPD). Human bronchial epithelial cells (HBEcs) are key effector cells in the pathogenesis of COPD, making them essential for assessing the comorbid association of COPD with CKD. The objective of this study was to investigate the impact of hyperphosphatemia and COPD on bone turnover.

Methods: HBEcs were treated with 1 to 5 mM sodium phosphate, FGF23, and/or cigarette smoke extract (CSE). Expression levels of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and IL-8 were analyzed by RT-qPCR. Concentration of these cytokines in serum was also quantified via enzyme-linked immunoassay (ELISA). In addition, wild type and FGF4 knockout (FGF4−/−) mice were fed a high phosphate diet for a total of three months or exposed to cigarette smoke for three weeks. Lung tissue was then analyzed by western blotting and RT-qPCR.

Results: Increased phosphate concentrations induced an inflammatory response in HBEcs, which was further exacerbated by the addition of CSE but attenuated by Foscarnet treatment. Furthermore, mice on a high phosphate diet showed increased FGF-23 and IL-6 levels in their lung. The increase in IL-6 was not observed in the FGF4−/− mice. Subacute cigarette exposure led to an increase in IL-1β and IL-8 in total lung tissue, which was abrogated in the FGF4−/− mice.

Conclusions: Our in vivo data suggest that CKD-associated hyperphosphatemia may contribute to the development of airway inflammation, whereas our in vivo data demonstrate a role of both phosphate and FGF23 signaling in mediating lung inflammation. In summary, our results show that in CKD, there seems to be kidney-lung crosstalk with both FGF23 and phosphate as mediators of an inflammatory airway response, which seems to be mediated by FGF4R.

PO0535
Plasma Biomarkers of Mineral and Bone Disorder in ADPKD Patients Treated with Tolvaptan
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Background: Autosomal-dominant polycystic kidney disease (ADPKD) is characterized by a unique bone and mineral phenotype. Patients affected by ADPKD show parathyroid hormone (PTH) resistance, a better-preserved cortical bone mass, higher sclerostin levels, lower bone turnover and total alkaline phosphatase compared to other chronic kidney disease (CKD) astologies. To date, the association between tolvaptan administration, plasma biomarkers of mineral and bone disorder (CKD-MBD) and bone mineral density has not been investigated.

Methods: We conducted an analysis of patients enrolled in the Bern ADPKD registry, a prospective observational cohort study. Plasma parameters for CKD-MBD and 24-hour urine analyses were performed at baseline and every 12 months thereafter. DXA scans were obtained at baseline and after 3 years. Multivariable fixed-effects regression models were applied for sex, BMI, FGF23 (a marker of acid intake) and NGAL (a marker of alkl intake) were applied to study changes in CKD-MBD parameters and bone mineral density associated with tolvaptan treatment.

Results: A total of 167 participants (56 with and 111 without tolvaptan treatment) were included in the analysis. Median follow-up time was 24.5 months. After adjusting for potential confounders, tolvaptan treatment was associated with a significantly reduced plasma PTH (β = -14.84; 95% CI, -28.61 to -1.07; p = 0.04), increased total plasma calcium (β = 0.05; 95% CI, 0.01 to 0.09; p = 0.01), plasma magnesium (β = 0.02; 95% CI, 0.00 to 0.04; p = 0.04) and feraloral but not lumbar bone mineral density (β = 0.10; 95% CI, 0.01 to 0.19; p = 0.04 and β = 0.22; 95% CI, -0.04 to 0.08; p = 0.49, respectively). In contrast, tolvaptan treatment was not associated with changes in plasma phosphate, ionized calcium, TmP/GFR, serum intact fibroblast growth factor 23, plasma alkaline phosphatase, blood pH or serum 1,25(OH)2 and 25(OH) vitamin D.

Conclusions: Tolvaptan treatment is associated with changes in mineral metabolism parameters and increased bone mineral density at the femoral neck. Long-term prospective studies are needed to assess the impact of tolvaptan on fracture risk.

PO0536
Call for Harmonization of the Histomorphometric Reference Ranges for Bone Turnover in Renal Osteodystrophy
Hanne S. Joergensen,1,2 Patrick D’Haese,2 Geert J. Bechets,3 Etienne Cavalier,4 Pieter Evenepoel,7 on behalf of the EUROID initiative of the CKD-MBD working group of the European Renal Association and European dialysis and transplantation (ERA-EDTA), 1Aarhus Universitetshospital, Aarhus, Denmark; 2Universiteit Antwerpen, Antwerpen, Belgium; 3Universite de Liege, Liege, Belgium; 4Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven, Leuven, Belgium.

Background: Knowledge of bone turnover helps guide fracture preventive treatment in patients with chronic kidney disease (CKD). Bone histomorphometry remains the gold standard to assess bone turnover, while non-renal-retained bone biomarkers are considered a valid, but imperfect alternative. Published reports show marked variations in the histomorphometric reference values of bone turnover. Our aim was to investigate the impact of different diagnostic cutoffs on the categorization of bone turnover in a CKD population.

Methods: 199 patients with successful bone biopsies before or after kidney transplantation were categorized for bone turnover according to diagnostic cutoffs as published by Salusky et al and Malluche et al, recently published normative histomorphometric data by Recker et al, as well as population-based normal ranges for bone-specific alkaline phosphatase (BSAP), tetrarositate-resistant acid phosphatase type 5b (TRAP5b), and trimeric procollagen type I N-terminal propeptide (Intact PINP, all IDS-isYS).

Results: Major differences in the distribution of bone turnover categories were seen depending on the reference category of cutoffs. Pi-tol acetate inhibited kidney transplant candidates (n = 80, Figure) and recipients (n = 119, data not shown). Compared to the categorizations based on biochemical bone turnover markers, the bone biopsy diagnosis was skewed toward lower bone turnover when using cut-off as proposed by Salusky or Malluche.

Conclusions: These findings call for harmonization and calibration of bone histomorphometry for the categorization of bone turnover. This will require a collaborative effort to first, construct a repository of bone histomorphometric data from healthy controls across ages, sexes, and ethnicities, and second, to reach a consensus on the diagnostic cutoffs for bone turnover in renal osteodystrophy.
Effects of Patiromer on Serum Phosphate over 4 Weeks of Treatment in Hyperkalemic Patients with Hyperphosphatemia: Pooled Analysis of the AMETHYST-DN, OPAL-HK and TOURMALINE Trials

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Background: Elevated serum phosphate (sP) is associated with increased mortality in non-dialysis CKD. KDIGO guidelines suggest elevated sP should be lowered into the normal range: 2.5–4.5 mg/dL. Patiromer is a non-absorbed, sodium-free, potassium (K+) binder that uses calcium as the exchange ion which, when released, likely binds to intestinal phosphate. We conducted a post-hoc analysis of pooled data from AMETHYST-DN, OPAL-HK and TOURMALINE to evaluate patiromer’s effect on sP over 4 weeks in patients with sP >4.5 mg/dL.

Methods: Eligible patients had CKD and hyperkalemia (HK; serum K+[sK+] ≥5.0 mEq/L). Prescription of phosphate binders was not allowed. Hyperphosphatemia subgroup was defined as baseline sP >4.5 mg/dL. Patients in the analysis received ≥1 dose of patiromer (8.4–33.6 g/day to start) and had ≥1 post-baseline sP assessment. Mean (±SD) changes from baseline in sP, sK+, serum magnesium and serum calcium at weeks 2 and 4 were evaluated.

Results: 86/578 (15%) patients had baseline sP >4.5 mg/dL. 36% were male, mean (SD) age was 63.9 (10.5) years, 84% had diabetes, mean (SD) eGFR was 25.9 (17.2) mL/min/1.73m² and 76% had stage 4/5 CKD. Mean (SD) baseline sP and K+ were 5.0 (0.5) mg/dL and 5.5 (0.4) mEq/L, respectively. At 2 or 4 weeks of patiromer treatment, both mean sP and sK+ levels decreased into the normal range (Table). Most frequent adverse events (AEs) included gastrointestinal events (6/86; 7%); most cases were mild or moderate in severity. AEs leading to discontinuation occurred in 3/86 (4%) patients.

Conclusions: Patiromer decreased both sP and sK+ into the normal range in patients with elevated sP and sK+. Patiromer was well tolerated with mild/moderate gastrointestinal events. The ability of patiromer to normalize sP may be therapeutically useful in hyperkalemic patients with HK and hyperphosphatemia.

Funding: Commercial Support - Vifor Pharma Ltd

Table: Serum phosphate, potassium, calcium, and magnesium at baseline, after 2 and 4 weeks of patiromer treatment

PO0538

Circadian Changes in Serum Phosphate Among Patients with ESKD on Hemodialysis

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Background: Serum phosphate concentrations are known to have a circadian rhythm in healthy adults and in CKD, with a nadir in the late morning and a peak in the afternoon. Circadian changes in serum phosphate concentrations among persons on chronic hemodialysis may have important treatment implications, as serum phosphate concentrations are a therapeutic target in these patients.

Methods: We assessed serum phosphate concentrations in 118,440 persons with ESKD treated with in-center hemodialysis at Fresenius Kidney Care centers across the United States in July 2017. We used linear regression to assess the relationship between time of day and serum phosphate concentrations. We assessed unadjusted models and models adjusting for age, sex, race, region, weight, diabetes and use and dose of vitamin D analogs, calcitominics and phosphate binders.

Results: The cohort had mean age 63 ± 13 years, 44% were female, 53% were white and 33% were black. The mean serum phosphate concentration was 5.3 ± 1.5 mg/dL. In both the unadjusted and fully adjusted models, serum phosphate concentrations varied over the day with a peak at 6:00 pm and a nadir at 10:00 am (p < 0.001). In the unadjusted model the difference from peak to nadir was 0.6 mg/dL. This difference was attenuated in the fully adjusted model to 0.2 mg/dL (Figure).

Conclusions: In a large and diverse cohort of adults with ESKD treated with hemodialysis, serum phosphate concentrations varied depending on the time of day in which serum phosphate levels were measured. Thus, the target serum phosphate range for patients treated with hemodialysis should account for when serum phosphate is being measured.

Funding: NIDDK Support, Commercial Support - Fresenius Medical Care North America
PO0540

Pill Burden and Changes in Mineral Bone Disorder (MBD) Markers in Hemodialysis (HD) Patients Switched from Sevelamer to Sucroferric Oxyhydroxide (SO): A One-Year Follow-Up in a Contemporary Cohort

Meijiao Zhou,1 Linda Ficociello,1 Vidhya Parameswaran,1 Claude Mullon,2 Michael S. Anger,1,3 Fresenius Medical Care Global Medical Office, Waltham, MA; 1University of Colorado, School of Medicine, Denver, CO; 4Washington University School of Medicine, St. Louis, MO

Background: About 80% of US dialysis patients are prescribed phosphate binders (PB) for serum phosphorus (SP) control; however, PB high pill burdens are associated with non-adherence and elevated SP levels. Clinical and observational studies have demonstrated that SO is effective in lowering SP with similar efficacy to sevelamer (Sev), but with a lower pill burden. The present study aims to assess the long-term changes in MBD markers and pill burden in a contemporary HD cohort switching from Sev to SO.

Methods: The study included adult, Fresenius Kidney Care maintenance HD pts receiving Sev during a 91-day baseline (BL) and first prescribed SO monotherapy during 5/2018-5/2019. The one year follow up (FU) on SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Comparisons of PB pill burden and MBD markers between BL and FU were carried out using mixed-effects linear regression and Cochran’s Q test.

Results: On average, patients (n=841) were 56.2 (13.3) years old with dialysis vintage of 50.5 (48.6) months. At BL, the % of pts was 21.2% for SP ≤5.5 mg/dL and 4.5% for SP 4.5 mg/dL, with 8.4 Sev pills/day; after switching to SO, the % of patients increased to 35.4% - 44.0% for SP ≤5.5 mg/dL and 11.4% - 16.1% for SP 4.5 mg/dL with 4.4 - 4.9 pills/day. Mean iPTH and serum calcium (Ca) decreased progressively after SO conversion.

Conclusions: Maintenance HD patients switching PB prescription from Sev to SO during 2018 and 2019 as part of routine care showed significant reductions in SP and PB pill burden, and increases in the number of patients with SP ≤5.5 mg/dL and SP 4.5 mg/dL. A trend toward decreased serum Ca and iPTH levels during SO therapy was also observed.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO0541

Serum Phosphorus (SP) and Pill Burden Among Hemodialysis (HD) Patients Prescribed Sucroferric Oxyhydroxide (SO): One-Year Follow-Up on a Contemporary Cohort

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Background: A previous real-world analysis included HD patients (pts) prescribed SO during 2014-2015 followed for 1 year. Improvements in SP were observed along with fewer phosphate binder (PB) pills/day after pts switched from their previous PB to SO (2014 Cohort, Kendrick). To examine how PB prescription (Rx) patterns have changed over time, the present study compares the long-term effectiveness of SO in a contemporary cohort (prescribed SO in 2018-2019; 2018 Cohort) with 2014 Cohort results.

Methods: Adult Fresenius Kidney Care HD pts first prescribed SO monotherapy between 5/2018-5/2019 and were on SO therapy for 3 months (baseline; BL) before SO Rx. Mean PB pill burden were compared between BL and Q1-Q4, using mixed-effects linear regression and Cochran’s Q test.

Results: Patients (n=115) were on average 55.5 (12.6) years old with 52.8 (46.4) months HD vintage, 38% female, 54% had diabetes and 20% had CHF. There were consistent improvements in pts achieving SP ≤5.5 mg/dL (from 20% at BL to 35.7% - 44.3% with SO; p<.0001) and in patients achieving SP 4.5 mg/dL (from 6.1% at BL to 8.7% - 16.5% with SO; p=0.02). Pts were prescribed 6.7 pills/day at BL and 4.7-5.2 pills/day with SO. SO conversion was associated with decreases in mean iPTH (620 pg/ml at BL, 496 pg/ml at Q4, p<.0001) and serum calcium (9.18 mg/dl at BL, 8.93 mg/dl at Q4, p<.0001).

Conclusions: Maintenance HD pts switching PB presc from ferric citrate to sucroferric oxyhydroxide experienced significant increases in % patients achieving in-range SP (<111% for SP ≤5.5mg/dL and <144% for SP ≤4.5mg/dL) with a lower pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO0542

One-Year Follow-Up of Maintenance Hemodialysis (HD) Patients Who Switched Phosphate Binder (PB) Prescription from Ferric Citrate (FC) to Sucroferric Oxyhydroxide (SO)

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Background: A new class of iron based PBs have been prescribed to HD patients for hyperphosphatemia management. This one-year real-world data analysis in a contemporary cohort of HD patient who switched from FC to SO as part of routine care investigates changes in serum phosphorus (SP) and pill burden.

Methods: Adult Fresenius Kidney Care HD patients included in the analysis were first prescribed SO monotherapy between 5/2018-5/2019 and were on FC for 3 months (baseline; BL) prior to SO therapy. The one year SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Changes in lab measurements and PB pill burden were compared between BL and Q1-Q4, using mixed-effects linear regression and Cochran’s Q test.

Results: Patients (n=115) were on average 55.5 (12.6) years old with 52.8 (46.4) months HD vintage, 38% female, 54% had diabetes and 20% had CHF. There were consistent improvements in pts achieving SP ≤5.5 mg/dL (from 20% at BL to 35.7%- 44.3% with SO; p<.0001) and in patients achieving SP 4.5 mg/dL (from 6.1% at BL to 8.7%-16.5% with SO; p=0.02). Pts were prescribed 6.7 pills/day at BL and 4.7-5.2 pills/day with SO. SO conversion was associated with decreases in mean iPTH (620 pg/ml at BL, 496 pg/ml at Q4, p<.0001) and serum calcium (9.18 mg/dl at BL, 8.93 mg/dl at Q4, p<.0001).

Conclusions: Maintenance HD pts switching PB presc from ferric citrate to sucroferric oxyhydroxide experienced significant increases in % patients achieving in-range SP (<111% for SP ≤5.5mg/dL and <144% for SP ≤4.5mg/dL) with a lower pill burden.

Funding: Commercial Support - Fresenius Medical CareRenal Therapies Group

PO0543

Effects of Lanthanum Carbonate on Whole-Body Phosphorus Balance in Patients with Stage 3b-4 CKD and Normophosphatemia

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Background: In CKD, elevated phosphorus, even within the normal range, is associated with cardiovascular disease (CVD) and mortality. However, in normophosphatemic CKD, phosphate binders do not improve vascular function, an independent predictor of CVD. Whether long-term treatment with phosphate binders affects phosphorus balance in CKD is unknown. Our objective was to determine phosphorus balance in normophosphatemic subjects with CKD 3b-4 after 12 weeks of treatment with lanthanum carbonate (LC) or placebo.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Impact on Parathyroid Hormone (PTH) Levels
Etelcalcetide is a calcimimetic approved in 2017 for the control of secondary hyperparathyroidism in adult hemodialysis patients. Some US hemodialysis (HD) facilities switched from oral cinacalcet (Cina) to etelcalcetide (Etel) to control parathyroid hormone (PTH) levels after the introduction of Etel in 2017. While clinical trial data have indicated superior efficacy of Etel vs. Cina, real-world evidence is lacking.

Methods: We evaluated facility calcimimetic use during 6-month intervals before (Period 1: May-October 2016) and after (Period 2: March-August 2019) introduction of Etel using US-DOPPS data. We compared the pre-post difference in outcomes – PTH, Ca, P – over the 6 months after each exposure period among calcimimetic users in HD facilities that “switched” from treating >75% of calcimimetic users with cinacalcet (“Cina-first”) in Period 1 to treating >75% of calcimimetic users with etelcalcetide (“Etel-first”) vs. facilities that remained Cina-first in Period 2.

Results: Among 32 US HD facilities that switched to Etel-first in Period 2, mean PTH decreased from 671 to 484 pg/mL, and % PTH >600 pg/mL decreased from 39% to 21%. Among 34 facilities that remained Cina-first in Period 2, mean PTH increased from 632 to 698 pg/mL and % PTH >600 pg/mL increased from 37% to 43%. The adjusted difference-in-difference between switch to Etel-first and remain Cina-first was -169 (95%
Conclusions: In this natural experiment, we observed better PTH control in facilities that switched to etelcalcetide (vs. remained cinacalcet) as the primary calcimimetic therapy. Further research is needed to evaluate whether this clear difference in real-world effectiveness translates to a reduction in hospitalizations and mortality.

Funding: Other NIH Support - Agency for Healthcare Research and Quality (AHRQ), Commercial Support - This analysis was supported by Amgen. Other support included research funding from Astellas Pharma Inc., AstraZeneca Pharmaceuticals LP, Baxter Healthcare Corp, Bayer Yakuhin, Ltd, Chugai Pharmaceutical Co., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd.; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co,Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd

PO0547
A Real-World Observational Study of Calcimimetic Use in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT) in Europe

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Background: Calcimimetics, Cinacalcet (CIN) and Etelecalcetide (ETEL), are approved for treating SHPT in adult patients on maintenance HD. Data on real-world use are needed to guide clinical practice.

Methods: In this observational study, chronic HD patients treated with calcimetics for SHPT with a1 parathyroid hormone (PTH) measurement recorded within 90 days before calcimimetic initiation were included. Medical history, PTH, calcium (Ca) and phosphate (P) measurements, and calcimimetic use data were extracted from medical charts. Baseline period was defined as 6 months before calcimimetic initiation.

Results: Interim data for 974 HD (198 CIN and 776 ETEL) patients across 15 countries in Europe, recorded from June 2018 to March 2021, are reported. 43% (334/776) of ETEL patients had switched within 90 days after stopping CIN. ETEL patients were younger than CIN patients (median age: 62 vs. 65 yrs.). Dialysis vintage was longer for ETEL than CIN patients (median: 44 vs. 2 yrs.). Starting dose was 30 mg for 95% of CIN; and 5 mg for 42.5 mg for 45% and 40% of ETEL patients respectively. At 12 months, median PTH had decreased by 41% in ETEL and 31% in CIN patients (Table 1), however 54% of ETEL and 57% of CIN patients achieved target PTH range (150-600 pg/mL). The cumulative incidence of hypocalcemia (Ca <2.1 mmol/L) at 6 months (66% vs. 59%) was higher in CIN than ETEL patients but difference was recorded at 12 months (74% vs. 73%). As recorded in medical charts, nausea (2.2% vs. 2%) and vomiting (0 vs. 1.3%) were low for CIN and ETEL patients. ETEL persistence (88%) was greater than CIN (76%) at 12 months. 16% switched from CIN to ETEL and 2% from ETEL to CIN during follow-up.

Conclusions: ETEL and CIN patients achieved target PTH range to a similar degree at 12 months, however PTH decrease over time was better in ETEL patients. Treatment persistence was higher with ETEL than CIN. No new safety signals were observed.

Funding: Commercial Support - AMGEN

PO0548
Effects of Etelecalcetide on the Evolution of Cortical Porosity in Patients and Rats with CKD

Background: Suppression of chronically elevated parathyroid hormone (PTH) is a key treatment goal in patients with chronic kidney disease—mineral and bone disease (CKD-MBD). High PTH leads to increased cortical porosity which is associated to increased fracture risk. We tested the hypothesis that etelcalcetide, a calcimimetic agent, suppresses cortical bone porosity development in HD.

Methods: For our clinical cohort, etelcalcetide was dose-titrated to maintain serum PTH at 2-5 times the upper limit of normal of the local PTH assay, corresponding to the lower half of the KDIJO recommended target level. Patients were scanned at the distal tibia by high resolution peripheral QCT before and after 9-months of treatment. For our preclinical cohort, etelcalcetide was administered to an established model of progressive CKD (Male Cy+/+ rat) for 3-5 weeks with in vivo microCT scans at the distal tibia taken at baseline and endpoint. Clinical and preclinical scans were registered across the two time-points and cortical pores tracked for their dynamic action (filled, contracting, expanding, developed).

Results: Etelecalcetide significantly suppressed PTH in both the clinical (-64%) and pre-clinical (-77%) cohorts. Total cortical porosity did not increase over the course of treatment in either humans (baseline 5.8% vs. endpoint 5.8%) or rats (baseline 3.3% vs. endpoint 3.7%). However, changes were detected at the individual pore level by individual cortical porosity analysis. In humans, of the baseline pores, 3% were unchanged, 25% had completely infilled, 40% had become smaller and 27% had increased in size. Twenty-one percent of the total pores at end of treatment were formed de novo during treatment. In the preclinical data followed similar trends, 43% of baseline pores had completely infilled, 20% had decreased in size, 22% had increased in size and 63% of the total pores at end of treatment had formed de novo.

Conclusions: PTH suppression by etelcalcetide stabilizes overall cortical porosity yet permits dynamic activity of individual cortical pores during treatment. Further studies are needed to determine if de novo cortical porosity can be prevented by more aggressive PTH reduction.

Funding: Veterans Affairs Support, Commercial Support - Amgen
Baseline DXA parameters and Change in DXA parameters following treatment with etelcalcetide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (Mean±SD)</th>
<th>Change (Mean±SD)</th>
<th>p-value</th>
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<tr>
<td>Z-score Lumbar spine</td>
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<td>0.7±1.8</td>
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</table>

PO0550

Etelcalcetide Suppresses Trabecular and Cortical Bone Remodeling Without Altering Bone Quality in Patients with ESKD

Corinne E. Metzger,1 Matthew R. Allen,1 John G. Damrath,3 Rachel K. Surowiec,1 Joseph M. Wallace,1 Joshua C. Sung,1 Sanchita Agarwal,2 Thomas Nickolas.2 1Indiana University School of Medicine, Indianapolis, IN; 2Columbia University Irving Medical Center, New York, NY; 3Indiana University Purdue University at Indianapolis, Indianapolis, IN. 5

Background: A key treatment goal in chronic kidney disease-mineral and bone disease (CKD-MBD) is suppression of chronically elevated parathyroid hormone (PTH). High PTH in CKD is associated with high bone turnover and fracture risk. Calcimimetics, such as etelcalcetide, are pharmacologic agents used clinically to reduce PTH to target levels. The goal of this study was to test whether 9-months of etelcalcetide treatment suppress bone remodeling in patients with end stage kidney disease (ESKD) on hemodialysis with renal hyperparathyroidism (RHT).

Methods: Five patients were enrolled. Mean age was 52±16 yrs and 80% were female. A quadruple label method was used to quantify pre- and post-treatment effects of etelcalcetide on bone turnover and quality of bone treatment, patients were administered demeclocycline at the specified PTH level for 6 months. At end of treatment, demeclocycline was administered (3 days, 15 day interval, 3 days) followed by transiliac crest bone biopsy.

Results: Mean PTH (pg/mL) levels at baseline and 9-months were 616±135 and 284±120, respectively. Following 9-months of treatment trabecular bone formation rate was 80% lower (range of -54 to -96%) while intracortical rate was 83% lower (range of -61 to -94%). Suppressed remodeling of both trabecular and intracortical bone occurred through a reduction in both the amount of bone undergoing remodeling (~65%) and the mineralization phase (~35%). Static histomorphometry showed osteoclast surface (~1%) and eroded surfaces (5.5%) were within normal ranges. Raman and nano-indentation measures showed no differences in trabecular bone mineral/matrix properties between the two timepoints.

Conclusions: This work shows that etelcalcetide corrects high bone turnover in patients with RHTp on dialysis without affecting bone quality. More research is needed to determine whether the potent remodeling suppression by etelcalcetide can be used as a primary strategy to reduce risk of fracture in patients with ESKD.

Funding: NIDDK Support, Commercial Support - Amgen

PO0551

Interim Analysis of Paricalcitol vs. Cinacalcet in Hemodialysis Patients with Secondary Hyperparathyroidism: A Multicenter, Randomized, Positive Controlled Study (PERMIT Study)

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Background: High PTH in CKD is associated with high bone turnover and fracture risk. Calcimimetics, such as etelcalcetide, are pharmacologic agents used clinically to reduce PTH to target levels. The goal of this study was to test whether 9-months of etelcalcetide treatment suppress bone remodeling in patients with end stage kidney disease (ESKD) on hemodialysis with renal hyperparathyroidism (RHT).

Methods: Five patients were enrolled. Mean age was 52±16 yrs and 80% were female. A quadruple label method was used to quantify pre- and post-treatment effects of etelcalcetide on bone turnover and quality of bone treatment, patients were administered demeclocycline at the specified PTH level for 6 months. At end of treatment, demeclocycline was administered (3 days, 15 day interval, 3 days) followed by transiliac crest bone biopsy.

Results: Mean PTH (pg/mL) levels at baseline and 9-months were 616±135 and 284±120, respectively. Following 9-months of treatment trabecular bone formation rate was 80% lower (range of -54 to -96%) while intracortical rate was 83% lower (range of -61 to -94%). Suppressed remodeling of both trabecular and intracortical bone occurred through a reduction in both the amount of bone undergoing remodeling (~65%) and the mineralization phase (~35%). Static histomorphometry showed osteoclast surface (~1%) and eroded surfaces (5.5%) were within normal ranges. Raman and nano-indentation measures showed no differences in trabecular bone mineral/matrix properties between the two timepoints.

Conclusions: This work shows that etelcalcetide corrects high bone turnover in patients with RHTp on dialysis without affecting bone quality. More research is needed to determine whether the potent remodeling suppression by etelcalcetide can be used as a primary strategy to reduce risk of fracture in patients with ESKD.

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PO0552

The Impact of Paricalcitol on Parathyroid Gland Size of Secondary Hyperparathyroidism Patients with Long-Term Maintenance Hemodialysis: An Observational Study

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Background: This is an observational study to assess effectiveness of paricalcitol for treating secondary hyperparathyroidism (SHPT) patients with long-term maintenance hemodialysis, via changes in biochemical indexes, such as Calcium (Ca), Phosphate (P) and Parathyroid Hormone (PTH), and size of parathyroid gland (PG). The primary and secondary endpoints were the combination therapy rate, more than 30% or 50% of patients would be carried out when monotherapy was unable to meet the expected target for 11 months' treatment. Moreover, there were no significant changes in serum calcium and phosphorus levels during the whole treatment.

Conclusions: Intraintravenous paricalcitol can decrease the size and number of parathyroid gland, and reduce iPTH concentrations in SHPT patients with Long-term maintenance hemodialysis, without significant influence for serum Ca and P levels.

Fig 1: Study Design
PO0553

Burden of Secondary Hyperparathyroidism: A Matched Comparison Using Administrative Claims Data from Germany

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Background: Secondary hyperparathyroidism (SHPT) is a frequent, early, and progressive complication in chronic kidney disease (CKD) characterized by excessive parathyroid hormone production. SHPT independently predicts serious complications like cardiovascular diseases (CVD), fractures, progression to dialysis, and death. Analysis of data on the burden of CKD patients with SHPT in the German health insurance system is lacking.

Methods: A German health insurance claims database comprising data from 2014-2018 served as a source to identify CKD stage 3 and 4 patients, who were stratified by the occurrence of incident SHPT using ICD-10-GM diagnosis and ATC prescription codes. SHPT patients were matched 1:1 to non-SHPT patients in the same CKD stage using propensity scores. Index date was the first SHPT diagnosis quarter in the SHPT cohorts, and a randomly chosen quarter of a CKD diagnosis within the CKD-only cohorts. Patients with evidence of dialysis or kidney transplant prior to the index quarter were excluded. Matched groups were compared with respect to the prevalence of CVD (acute and recurrent myocardial infarction (MI), chronic ischemic heart disease, congestive heart failure (HF), and atherosclerosis (ATH)), dialysis, and CKD progression in a two-year follow-up period.

Results: Overall, 1,156 incident SHPT patients in CKD3 and 517 in CKD4 and the 2,313 matched controls were identified. Prevalence of combined CVD conditions was higher in SHPT patients (46.8% vs. 41.9% p=0.05 in CKD3, 56.5% vs. 51.8% p=0.13 in CKD4). HF was more frequent among SHPT patients (34.6% vs. 28.6% p=0.01 in CKD3 and 46.4% vs. 39.3% in CKD4 p=0.05) while acute MI was observed significantly more often among CKD4 patients in the SHPT cohort (9.1% vs. 5.8% p=0.05). ATH was more frequent in SHPT patients in CKD4 (18.6% vs. 14.3% p=0.06). SHPT patients progressed to CKD5 more often (6.1% vs. 1.2% from CKD3, 26.7% vs. 2.9% from CKD4, both p<0.01) which resulted in a higher proportion of dialysis (6.1% vs. 1.3% in CKD3, 22.1% vs. 3.7% in CKD4, both p<0.01).

Conclusions: Patients with CKD3&4 and incident SHPT presented with a significantly higher disease progression to CKD5 and dialysis and had a higher prevalence of CVD compared to patients without SHPT during a two-year follow-up period.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma Ltd.

PO0554

Abstract Withdrawn

PO0555

Calcium-Based Phosphate Binders and the Regulation of FGF-23

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Background: Phosphate and calcium load are associated with FGF23 increase. Reduction of intestinal phosphate absorption by Calcium-based binders (Ca-bB) should decrease serum FGF23, but the opposed effect may result from Ca-bB-administration. Since Ca-bB has been associated with vascular calcifications and FGF23 is an independent risk factor for cardiovascular disease (CVD), it is relevant to elucidate the effect of Ca-bB on FGF23. Thus, we aimed to determine the effect of Ca-bB on FGF23.

Methods: We included 121 prevalent HD patients. Serum phosphate, Ca, iPTH and intactFGF23 were measured. 52 patients were on Calcium-free (NoCa-bB) binders, whereas 69 were on calcium-based (Ca-bB, n=69) binders. We also considered treatments with cinacalcet, paricalcitol and the calcium dialysate content. Multivariable regression identified the variables associated with FGF23 increase. Statistics were performed using R.

Results: The mean age was 67.8±14.7. Serum levels of phosphate, Ca and iPTH were comparable between groups of binders (Fig 1A, B, and C). iFGF23 was higher in patients on Ca-bB than in NoCa-bB (2815.7±1268.09 pg/mL p<0.001). Multivariable regression, adjusted for iPTH, dialysate calcium, albumin, and the treatment with cinacalcet and paricalcitol, showed that the use of Ca-bB was associated with increased serum iFGF23 (beta=0.46, p<0.01).

Conclusions: At equivalent serum levels of serum phosphate, Ca, and iPTH, the use of Ca-bB is independently associated with higher serum iFGF23. This could partially explain the detrimental cardiovascular effects associated with Ca-bB use in HD patients.

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PO0556

Side Selective Renal Reduction of Intact and C-Terminal FGF-23

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Background: Relative abundance of FGF23 measured by the C-terminal (cFGF23), which measures both intact FGF23 and C-terminal fragments) vs intact (iFGF23) assays is higher in persons with higher eGFR. Mechanisms are unclear. Individuals with vascular disease often have asymmetric renal function. We compared side selective (R vs L) renal reduction of iFGF23 and cFGF23 within the same individual.

Methods: 162 patients were referred for renal angiography at Maastricht University, the Netherlands, for clinically suspected RAS. Participants were maintained off anti-hypertensive meds for 21 days. Blood samples were obtained from the aorta and right (RV) and left renal vein (LV), and renal blood flow was measured using 125I Xenon washout. Creatinine (Cr), cFGF23 (Immutopics), and iFGF23 (Kainos) were measured. Difference of side selective % reductions of each metabolite ([Aorta – (RV or LV)/Aorta]×100) was calculated among each participant. Mean “RV-LV metabolite reduction difference” was calculated across all participants.

Results: Mean age was 54±12 years, 54% were women, and all were white. Mean eGFR was 75±25 ml/min/1.73m2 and directly measured Cr clearance during angiography was 72±48 ml/min/100g. Median (IQR) aorta concentrations of FGF23 was 82 (59, 105) RU/mL, and intact FGF23 was 47 (37, 65) pg/mL. The mean difference in R vs. L Cr clearance was 6.0 ± 36.2 ml/min/100g. Side selective reduction differences of both FGF23 & iFGF23 were significantly related to side selective Cr reduction. Side selective phosphate reduction also associated with iFGF23 reduction independent of Cr reduction, but not cFGF23 (Table). Results were similar in models adjusted for age, sex & BMI.

Conclusions: In hypertensive individuals, the kidney with greater Cr reduction also reduced plasma cFGF23 and iFGF23 more than the contralateral kidney. The kidney that removes more iFGF23 also removes more phosphate, independent of Cr removal; a finding not observed for cFGF23.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Uppercase represents presenting author.
PO0557


Background: Advanced chronic kidney disease (CKD) is characterized by mineral and bone disorders (MBD) including elevated fibroblast growth factor 23 (FGF23). Recent studies in healthy subjects showed that potassium supplementation decreases FGF23. Here, we investigated whether potassium supplementation reduces FGF23 and other MBD parameters in patients with CKD.

Methods: We performed a post-hoc analysis of a 2-week open-label run-in phase from a clinical trial in patients with CKD stage G3b-G4 (NCT03235172). Patients received potassium chloride (KCl), 40 mmol/day. Baseline and post-treatment blood and urine samples were collected. Mixed model analyses were used to assess effects of potassium supplementation on MBD parameters.

Results: We included 135 patients in whom KCl supplementation increased plasma phosphate (from 1.0±0.2 to 1.1±0.2 mmol/L, P<0.001) and tubular phosphate reabsorption (from 0.64±0.20 to 0.69±0.20 mmol/L, P<0.001). KCl supplementation, when adjusted for estimated glomerular filtration rate, decreased terminal FGF23 (eFGF23) (from 140.5±21.4 to 131.5 [IQR 105.8–212.8] RU/mL, P<0.05), intact FGF23 (from 69.6 [IQR 46.6–107.1] to 62.9 [IQR 41.7–104.6] pg/mL, P<0.003) and vitamin D (72.5 [IQR 43.9–92.9] to 70.2 [IQR 44.2–90.1] nmol/L, P<0.001). Parathyroid hormone, plasma calcium, 24hrs urinary calcium excretion, α-Klotho, and IL-6 did not change. At baseline, 37 participants were vitamin D deficient (<50 nmol/L). The decrease in eFGF23 by KCl supplementation depended on baseline vitamin D status (P-interaction=0.03), and was present in vitamin D sufficient (147.2 [IQR 108.3–216.8] to 130.9 [IQR 105.5–218.0] RU/mL, P=0.03), while it was not in vitamin D deficient patients (131.5 [IQR 104.0–230.7] to 133.0 [IQR 106.8–211.0] RU/mL, P=0.32).

Conclusions: In this short-term interventional study, KCl supplementation reduced FGF23 and coincided with increased plasma phosphate levels and vitamin D. Reduction in eFGF23 by KCl was only present in vitamin D sufficient patients. Dietary potassium intake might decrease FGF23 levels and vitamin D status should be sufficient before FGF23 lowering strategies could be applied in patients with CKD.

PO0558

The Dietary Supplement Chitosan Lowers Serum Phosphorus in a Hemodialysis Patient Not Tolerating Prescription Binders

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Introduction: Chitosan is a chitin derived, non-toxic, biodegradable biopolymer that binds negatively charged molecules. It’s numerous industrial applications include food industries, agriculture, pharmaceutical industries, water treatment industries, etc. It’s numerous industrial applications include food industries, agriculture, pharmaceutical industries, water treatment industries, etc. In humans it is used as a dietary supplement for weight loss, purportedly binding negatively charged lipids and bile acids and preventing their absorption. Here we report the case of a dialysis patient who did not tolerate prescription binders and who was able to control her serum phosphorus level for over a year by taking 3.5g of Chitosan with meals.

Case Description: A 66 y/o woman with no prior medical history and not taking any medications presented with emphysematous pyelonephritis with bilateral obstructing staghorn calculi requiring intensive care and hemodialysis. Her initial serum creatinine was 18 mg/dL. She recovered from sepsis but continued to require dialysis after discharge. Her residual creatinine clearance was 7.9 mL/min six months after hospital discharge and 5.6 mL/min two years later. The patient tried several prescription phosphorus binders but eventually decided to stop all prescription medications because of gastrointestinal side effects. Since over a year ago, at the recommendation of her dietician, she purchased 500mg Chitosan tablets from the internet and used them like a phosphorus binder with meals, at a dose of 3.5 g per day. Her serum phosphorus levels have been stable and in a controlled range since (Figure 1). A quantitative analysis using urea kinetics to estimate phosphorus intake and removal reveals that Chitosan bind around 40 mg of phosphorus per gram, comparable to prescription binders.

Discussion: Chitosan acts as an over-the-counter non-calcium containing phosphorus binder that may provide an alternative option for patients who do not tolerate prescription phosphorus binders. Importantly, it may be psychologically more attractive for patients to take a dietary supplement for weight loss with their meals than a prescription medication.

Figure 1: Effect of Chitosan on serum phosphorus levels

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0560

Two Siblings with X-Linked Hypophosphatemia (XLH) Treated with Burosumab: Is Therapeutic Regimen Recommended Now Supported by Real-World Data? 

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Introduction: Burosumab, a human monoclonal antibody to FGF23, is used now to treat XLH. In phase III study, patients were selected and controlled. What is considered as "recommended" regimen of burosumab in that population within the controlled setting might be different from that in another population in real world. The present study was conducted in an attempt to address this issue.

Case Description: Patient A and patient B with XLH are siblings in their twenties. They were successfully managed in childhood, and have enophosphatemia. They had had alpha calciferal and phosphate supplementation, and started to have 1 mg/kg BW burosumab 1.5 years ago. Changes in TmP/GFR, IP, and sCR after burosumab administration are shown (Figure). A significant increase in TmP/GFR (p<0.00001) was seen. IP and sCR levels almost did not change. Nephrocalcinosis, hyperparathyroidism, and vitamin D deficiency were mild and not worsened. Changes in bone mineral density (BMD) were assessed by DEXA scan. In 2018, young adult mean (YAM) of tibia vertebra were 129% in Patient A, and 138% in Patient B. In 2021, these YAM values increased to 141% in Patient A and 140% in Patient B, respectively.

Discussion: Using real-world data, we confirmed the efficacy and safety of recommended burosumab therapy regimen for 1.5 years, so far as laboratory indices used in phase III study were concerned. However, YAM values were above-the-average and increasing in the presence of hypophosphatemia and low TmP/GFR. The future consequence of this feature in relation to time-elapsed changes in renal physiological parameters including TmP/GFR, Ca, IP, and sCR should be seen.

PO0562

Regional Epidemiological Investigation of Calciphylaxis in Chinese Hemodialysis Patients

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Background: Calciphylaxis (calciific uremic arteriolopathy, CUA) is a grievous life-threatening vascular disease that commonly affects dialysis patients. This is the first epidemiological survey of CUA initiated in China.

Methods: In the cross-sectional survey during Oct. 2018 to Oct. 2019, a stratified sampling method was used to select 24 dialysis centers in Jiangsu Province in China. The participants were all adult patients in each center, who had been on hemodialysis for more than 6 months. This multicenter investigation was conducted in the form of questionnaires, which were filled in by doctors or nurses according to the actual situation of patients. CUA patients were uniformly diagnosed by the Calciphylaxis Study Group based on characteristic skin lesions and histopathological features.

Results: A total of 3867 hemodialysis patients (average age of 55.3±18.9 years; 61.81% of males) were included. 48 cases were diagnosed with CUA, and the prevalence was 1.24%. Among CUA patients, 68.75% of cases were male, and average age and median dialysis duration were 53.85±15.17 years and 84.00 (48.00, 136.75) months respectively. The average BMI of CUA patients was higher than that of controls, and patients with hyperparathyroidism, diabetes, atrial fibrillation, stroke, or tumors were more likely to suffer from the disease. Although only 4 CUA patients used warfarin therapy, there was still a significant statistical difference between two groups. Multivariate analysis indicated that increased BMI, prolonged dialysis duration, warfarin therapy, concomitant with hyperparathyroidism, diabetes mellitus or tumors, low ALB, and high serum ALP levels were high-risk factors for CUA. 394 (10.32%) of 3819 hemodialysis patients who didn't meet current diagnostic criteria for CUA had a variety of manifestations of skin lesions, mainly in lower limbs. 28.6% of these patients complained about a progressive deterioration of skin damage, and 44.67% suffered moderate to severe pain with potential CUA risks.

Conclusions: The prevalence of CUA in Chinese hemodialysis patients was 1.24% according to this regional epidemiological survey, but its actual prevalence would be presumably far beyond present data. Calciphylaxis, as a disease with such a high disability and fatality rate, should attract the attention of relevant specialists.

PO0563

Intraperitoneal Sodium Thiosulfate: Revisiting Route of Therapy for Calciphylaxis in Peritoneal Dialysis

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Introduction: Intraperitoneal (IP) drug therapy provides a convenient route for medication administration in patients on peritoneal dialysis (PD). IP sodium thiosulfate (STS) has been used for treatment of calciphylaxis with demonstrated enhanced calcium extraction. However, the use of this therapy has been limited after a reported incident case of chemical peritonitis. This reported complication did coincide with an FDA recall for...
STS, and the possibility remains that peritonitis may have been due to particulate matter contamination. We present a case of calciphylaxis which was successfully treated with IP STS without evidence of peritonitis.

Case Description: An 80 yo woman on PD presented with bilateral lower extremity pain and erythema. This progressed to a necrotic eschar (Figure 1A). Labs were notable for PTH 1267, and Ca x Phos product of 110. Biopsy confirmed calciphylaxis. She underwent subtotal parathyroidectomy and was treated with IV STS. Severe nausea with IV infusions necessitated discontinuation of therapy. She transitioned to IP therapy, 12.5 g of STS in 1L of normal saline as a long dwell day-time exchange to maximize absorption and subsequent mobilization of calcium from tissue. The patient’s pain significantly improved within 1 week. Therapy was completed after 3 months. The lesions almost completely healed 6 months after starting treatment (Figure 1B). Interval PD effluent cell counts, on several occasions, did not change in the PD effluent, although a modest, unexplained decrease in kt/V was noted.

Discussion: The use of IP medications in patients on PD minimizes venous access complications and reduces clinic visits. In our case, we were able to effectively treat calciphylaxis in a patient who could not tolerate IV STS therapy. No inflammatory activity appeared in the PD fluid, and it is unclear if STS had any other adverse effects. Further studies are needed to understand the impact of this therapy on peritoneal membrane transport characteristics.

PO0564
Calciphylaxis in a Cohort with Normal Kidney Function: Improved Survival Compared to ESKD
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Background: Calciphylaxis is a rare, devastating disease, characterized by vascular calcification and is associated with increased mortality.

Methods: We studied the baseline characteristics and outcomes of 78 patients with biopsy-proven calciphylaxis that were stratified according to glomerular filtration rate (GFR) into normal kidney function (NKF): GFR >15 mL/min/1.73 m²; chronic kidney disease (CKD): GFR 15 – 89 mL/min/1.73 m²; and end-stage kidney disease (ESKD): GFR <15 mL/min/1.73 m².

Results: Forty-seven patients (60%) with calciphylaxis had ESKD, compared to 22 patients (28%) with CKD and 9 patients (12%) with NKF. Patients with NKF were younger (median age 55 years compared to 69 years in CKD and 65 years in ESKD, p=0.006). Across all 3 groups, there was a predominance of female gender, obesity, multiple and peripheral lesions involving the extremities. Among patients with ESKD, 39 patients (83%) were on hemodialysis (HD) and 7 patients (15%) were on peritoneal dialysis (PD). The probability of survival was significantly higher in patients with NKF compared to ESKD (p = 0.039)(figure 1). Sepsis was the most common cause of death.

Conclusions: Calciphylaxis can occur in patients with normal or abnormal kidney function. Female gender, obesity, multiple, and peripheral lesions were predominant in our cohort. Patients with NKF were younger, which may have contributed to their increased survival compared to ESKD. Sepsis due to secondary infection of necrotic wounds appears to remain the most common cause of death.

PO0565
Severe Tumoral Calcinoses of the Hip in a Hemodialysis Patient

Introduction: Tumoral calcinoses (TC) is a rare complication of patients with end-stage renal disease (ESKD) on hemodialysis (HD) in which precipitation of calcium salts occurs in periarticular soft tissue. This manifestation can lead to painful and function restricting lesions. We herein describe a case of a severe presentation of TC with associated ulceration.

Case Description: A 47-year-old female with medical history of arterial hypertension, hyperlipidemia, hypothyroidism, focal segmental glomerulosclerosis and ESRD on HD for 15 years presented to the emergency department after a right hip ulceration. The patient described a right hip hard mass with ten years of progressive growth that suffered a sudden rupture associated with sand-like secretions. Medication and dialysis compliance was reported. Vital signs were unremarkable. Physical examination showed a right hip swelling and ulcer. Laboratories revealed WBC of 19.98 10³/µL, Hgb of 8.70 g/dL, calcium 9.9 mg/dL, phosphorus 6.6 mg/dL, 25-hydroxyvitamin D 12.72 ng/mL and PTH 288.90 pg/mL. Calcium Phosphate Product (CPP) resulted in 65.34 mg/dL. Pelvic CT scan showed a 11.4cm x 9.6cm mixed density calcified cystic mass with multiple fluid–calcium levels in the right hip, suggestive of TC. Treatment with intravenous Sodium Thiosulfate, Sevelamer and antibiotics were provided. Cleansing and debridement were performed by the plastic surgery team without complications. Patient was discharged and sodium thiosulfate treatment was continued at the hemodialysis center.

Discussion: TC is associated with the dysregulation of calcium phosphate metabolism. Altered renal phosphate excretion along with vitamin D activation leading to hyperparathyroidism with elevated CPP is the proposed mechanism. The precipitation of large periarticular deposits of calcium salts leads to inflammation and chronic pain. Consequently, limiting functionality and impairing quality of life. Surgical excision can relieve symptoms, but the deposits can recur. Sodium thiosulfate has been described as a potential treatment, but further studies are necessary to assess its role in dialysis patients.

The recognition of this rare disease is important as optimization of medical therapy and dialysis regimen can improve the evolution and outcome of this disorder.

PO0566
Case Series of Penile Calciphylaxis in a Large Urban Hospital
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Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a complex syndrome of deranged mineral metabolism and vascular calcification with subsequent tissue ischemia predominantly in end stage kidney disease (ESKD) patients on dialysis. The disease has been categorized as central or peripheral but in rare cases of peripheral calciphylaxis there may be penile involvement. Due to the paucity of data on penile calciphylaxis, this study was done to ascertain the characteristics, management and mortality of patients with this condition.
Methods: An observational study involving retrospective analysis of medical records of six (6) patients with biopsy proven penile calciphylaxis treated in a large urban hospital between January 2000 and March 2021 was performed.

Results: All patients with penile calciphylaxis had ESKD with mean duration on dialysis of 5.2±3.5 years. The mean age at diagnosis was 54±9.7 years. Sixty six percent of patients were African Americans with the remainder being Caucasians. Only one of six patients was obese with mean BMI of 23.2±5.5 kg/m². Similarly only one patient was on warfarin. None of the patients was on systemic steroids or vitamin D at the time of diagnosis. All patients had secondary hyperparathyroidism with median PTH of 264.5pg/mLwarfarin. None of the patients was on systemic steroids or vitamin D at the time of diagnosis. of 36.1
11.6mg2/dL2(normal range for our lab is 21.5-51.5). Penectomy was performed in 4 patients and 2 patients had treatment with hyperbaric oxygen. The mean survival at diagnosis was 4.0±1.2 months. Mortality was 20% and 100% at 3 and 6 months post diagnosis respectively.

Conclusions: Penile calciphylaxis is a very rare entity. Although obesity has been associated with calciphylaxis, majority of our patients with penile calciphylaxis were not obese. Interestingly all our patients had normal calcium phosphate products suggestive of heterogeneous mechanisms in the pathophysiology of the disease. The PTH was lower than our previously reported level of 569pg/mL in our calciphylaxis database. of heterogeneous mechanisms in the pathophysiology of the disease. The PTH was lower than our previously reported level of 569pg/mL in our calciphylaxis database. We present a case of a 33 year-old African American male with end-stage renal disease on maintenance hemodialysis x3/week for 7 years and systemic lupus erythematosus on adalimumab, who presented with sudden onset severe facial swelling and pain. He has a history of tertiary hyperparathyroidism with intact parathyroid hormone level of 2,400 – 4,000 pg/mL (normal: 18.4 - 88.0 pg/mL). Cinacalcet (30 mg) dosing was inconsistent due to insurance difficulties. Laboratory studies showed a corrected serum calcium of 7.9 mg/dL, serum 25-hydroxy-vitamin D of 9.8 ng/mL (25.00 - 80.00 ng/mL), serum phosphorus of 5.9 mg/dL, intact parathyroid hormone of 1,206 pg/mL and alkaline phosphatase 427 U/L (35-150) with normal liver enzymes. The patient had severe facial pain, maxillary and mandibular enlargement with hypertrophic gums and widely-spaced teeth. Extensive brown tumor formation was detected with marked extension into the buccal spaces. Altogether, his presentation was consistent with an unusually severe Sagliker syndrome. Urgent subtotal parathyroidectomy was performed with immediate normalisation of PTH (170, 75 pg/mL), but with subsequent severe postoperative hungry bone syndrome and a prolonged period of excessive calcitriol and calcium supplementation. At 2 year follow-up laboratory studies revealed corrected serum calcium of 7.5 mg/dL, serum phosphorus of 6.2 mg/dL, and intact parathyroid hormone of 36 pg/mL. While his facial abnormalities and pain improved, severe mandibular swelling persisted.

Discussion: Genetic predisposition may be related to target exons of calcium-sensing receptors. Low vitamin D levels are thought to play a role in susceptible patients. Our case presents a rare documented long-term outcome for severe Sagliker syndrome. Furthermore, we are reviewing initial and follow-up pictures, with review of biochemical control and vitamin-D requirements over this period.

PO0569

Incident Diuretic Use and Subsequent Risk of Bone Fractures: A Large Nationwide Observational Study of US Veterans

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Background: Diuretics may affect bone metabolism by electrolyte imbalance (e.g., Ca and Na derangements). Inconsistent associations have been reported between diuretic use and fracture, presumably due to the heterogeneity of study designs and populations.

Methods: In a nationwide cohort of 2,318,267 US veterans with an eGFR<60 mL/min/1.73m² from 2004-2006 and follow-up through 2018, we examined the association of incident diuretic use (thiazide, loop, and K-sparing diuretics, as time-dependent exposures) with incidence of any fractures (both vertebal and non-vertebral fractures), using time-dependent Cox models adjusted for sociodemographics, smoking and alcohol use, comorbidities, eGFR, vital signs, and medications (e.g., bone anabolic/antiresorptive agents, SERMs, steroids). Associations were also assessed by diuretic types.

Results: Patients were 58±15 years old; 91% were male; 14% were African American; and 18% were diabetic. Their baseline eGFR was 82±16 mL/min/1.73m². Among 2,318,267 patients, 835,054 (36.0%) started any diuretic therapy, and 146,017 (6.3%) experienced an incident fracture. After multivariable adjustment, incident diuretic use (vs. non-use) was significantly associated with higher risk of incident fracture (adjusted HR [95%CI], 1.13 [1.06-1.19]). The association was most pronounced for loop diuretics (1.37 [1.28-1.46]) but less evident for thiazide diuretics (1.07 [1.00-1.14]), and was not significant for K-sparing diuretics (1.16 [0.88-1.54]) (Figure).

Conclusions: Diuretic use, particularly loop diuretic use, was independently associated with higher risk of incident bone fractures. While our findings may be from confounding by medical indication, it might suggest a distinct pathogenic contribution of diuretics to bone metabolism and the need for careful attention to skeletal outcomes when initiating diuretics.

Funding: Veterans Affairs Support
PO0570

Low Magnesium Is Associated with Weak Bone Strength in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: In patients with chronic kidney disease (CKD), bone strength was weakened as CKD progressed. There are still controversy of the association between magnesium (Mg) deficiency and osteoporosis in pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and a decrease of bone mineral density (BMD) from the prospective, multicenter cohort of pre-dialysis CKD patients (n=928). Patients were divided into tertiles according to serum Mg. The primary endpoint is a decrease of BMD, defined as decline of BMD of lumbar spine ≤−0.05/cm²/year. We performed sensitivity analysis with decline of BMD of femur neck.

Results: After 4 years of follow-up, BMD decrease in 267 (28.7%) patients. In a multivariable binary logistic regression model, the lowest tertile of Mg was associated with risk of the decrease of BMD of lumbar spine (T1, serum Mg ≤2.2 mg/dL, Odd ratio (OR) 2.79 [1.58–4.92] vs T3, serum Mg ≥2.99 mg/dL, reference group). Similar results were obtained when sensitivity analysis was performed with BMD of femur neck. Subgroup analyses showed that low Mg was particularly associated with risk of the decreased BMD of lumbar spine in patients <50 years of age, in those without diabetes mellitus, and in those with low physical activity.

Conclusions: Low level of Mg is associated with a weak bone strength in pre-dialysis CKD patients.

PO0571

The Vitamin D Metabolite Ratio May Serve as an Important Biomarker of Vitamin D Status in Patients Undergoing Therapeutic Plasma Exchange

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Background: Recent studies suggest that 25-hydroxyvitamin D [25(OH)D] may be a poor marker of vitamin D status due to variability in levels of vitamin D binding protein (VDBP). The vitamin D metabolite ratio (VMR) is the ratio of 24,25(OH)D3:25(OH)D and is thought to be independent of variability in VDBP. Therapeutic plasma exchange (TPE) is a procedure that removes VDBP and thus may lower vitamin D metabolites. The effects of TPE on free vitamin D concentrations and the VMR remains unknown.

Methods: We measured total 25(OH)D, 1,25(OH)2D, 24,25(OH)2D3 and VDBP using Liquid chromatography–mass spectrometry, and free 25(OH)D using a DiaSource ELISA assay in 45 patients undergoing TPE. Levels were measured before and after a single TPE. We used the paired t-test to assess changes in 25(OH)D, 1,25(OH)D, 24,25(OH)D3, and free 25(OH)D. There was no change in the VMR from before to after TPE (Table 1).

Conclusions: Changes in VDBP concentration across TPE parallel changes in 25(OH)D, 1,25(OH)D, and 24,25(OH)D3 suggesting that levels of these metabolites may be markers of VDBP levels. The lack of change in VMR across TPE despite a significant change in VDBP suggests that VMR is independent of VDBP levels. The VMR may therefore serve as an important biomarker of vitamin D status in populations with a large spectrum of VDBP concentrations.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Changes in Vitamin D Metabolites, VDBP, and VMR from Before to After a Single TPE Procedure (N=45)

PO0572

Childhood Hypercalciciuric Hypercalcinemia with Elevated Vitamin D and Suppressed Parathyroid Hormone: Long-Term Follow-Up

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Background: Hypercalciuria with low parathyroid hormone (PTH) level, hypercalcemia, nephrocalcinosis, or nephrolithiasis, was recently reported as caused by mutations in CYP24A1 and SLCA34A genes. These encode for vitamin D-24A-hydroxylase and for the renal phosphate transporters NaPiIIa and NaPiIIc, respectively. We aimed to describe the course of these conditions during long-term follow-up

Methods: Ten patients with the above features were followed in our center during 1998-2019. Relevant laboratory and imaging data and results of genetic evaluation were retrieved from medical files.

Results: The median age at presentation was 9.5 months (range 1 month-11 years), six (60%) females, and the median follow-up time was 3.8 (1.1-14) years. Mutations in CYP24A1 and SLCA34A were identified in one and three patients, respectively. Five patients presented with nephrocalcinosis, three with nephrolithiasis, and two had normal renal ultrasound. High blood calcium and 1,25-(OH)2D levels at presentation decreased during follow-up (11.1±7 vs 9.9±0.5 mg/dl (p=0.012), and 307±230 vs 209±65 pmol/l (p=0.03), respectively); this paralleled an increase in suppressed PTH levels (5.8±6.9 vs 11.8±7.5 pg/ml, p=0.2). Substantial improvements in hypercalciuria and renal sonography findings were not observed. Two patients had impaired renal function (eGFR 84-88 ml/min/1.73m2) at the last follow-up. Interventions included appropriate diet, citrate supplementation, and thiazides.

Conclusions: In patients with the described clinical and laboratory profile, abnormal renal sonographic findings can persist despite appropriate treatment; and renal function may deteriorate. Long-term follow up and intervention to prevent nephrocalcinosis and nephrolithiasis are recommended in these children.

PO0573

Performance Status (PS) as an Effect Modifier for Association Between Vitamin D Receptor Activator (VDRA) and Outcomes Among Hemodialysis Patients

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Background: VDRA use has been reported to be associated with lower mortality and fracture among hemodialysis patients. However, PS has not been considered in previous studies.

Methods: This is a prospective cohort study based on JSDT Renal Data Registry. Subjects on hemodialysis with age 20-100 at the end of 2009 were included. Exposure variables were two-year all-cause mortality and hip fracture. Associations between VDRA use and mortality or fracture were analyzed using Cox or poisson regression, respectively and interaction between VDRA use and PS was tested.

Results: Among 210.001 subjects, 80,492 (67.7%) were on VDRA. VDRA use was not associated with all-cause mortality (HR 1.02 [0.99-1.05]) or hip fracture (IRR 0.93 [0.86-1.00]) after adjustment for confounders including PS. The use of VDRA was associated with lower mortality and incidence of fracture of those with good PS (HR 0.82 [0.78-0.86]) but not with poor PS (HR 0.97 [0.89-1.05], respectively). Poor PS was associated with higher corrected calcium (Ca), lower parathyroid hormone (PTH) levels, and proportion of intravenous VDRA use was lower among those with poor PS. Linear regression analysis showed that the association between higher corrected Ca levels and VDRA use were stronger among those with poor PS compared with those with good PS (interaction 0.01).

Conclusions: VDRA use was associated with better outcomes only among those with good PS. The reasons may be higher prevalence of adynamic bone among those with poor PS suggested by lower Ca levels and greater increase in Ca levels by VDRA, or preclusion of higher dose VDRA prescription due to higher Ca levels.
Prescription Patterns of Osteoporosis Medications in Patients with CKD Stages 4-5: A Retrospective Cohort Study

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Background: Vitamin D insufficiency and deficiency are common abnormalities and high risk groups include kidney disease patients and African-Americans. Recommendations on the evaluation of vitamin D levels in CKD and ESKD are ambiguous due to a lack of studies examining epidemiology and treatment. The COVID-19 pandemic has disproportionately affected minorities and has highlighted the need for evidence as studies have examined vitamin D deficiency as a risk factor for COVID-19 complications. We present a case series examining the prevalence of vitamin D deficiency in a predominantly African-American hemodialysis patient population.

Methods: Retrospective chart review of all in-center hemodialysis patients at Emory Dialysis in Atlanta, GA. Data extracted from Sep to Nov 2020. We excluded any patients on home therapies. Serum 25(OH) vitamin D concentration total was analyzed. We defined vitamin D insufficiency as 20-29.9 ng/mL and vitamin D deficiency as a level<20 ng/mL.

Results: Patients receiving in-center hemodialysis (n=615). Average length of time on dialysis was 5 years and average age was 59.4 years. Patients were 52.5% male(n=323), 91.5%(n=563) of patients were African-American. Mean calcium level for all patients was 8.73 mg/dL and PTH level of 554 pg/mL. Mean vitamin D in all patients was 26.32 ng/mL. 98%(n=603) of patients had a vitamin D level available. All patients with vitamin D level<30 ng/mL(412/68.3%) and all patients with vitamin D level<20 ng/mL(244/40.5%). African-American patients with a vitamin D level was 552. African-American patients with vitamin D level<30 ng/mL=382 (69.2%) and African-American patients with vitamin D level<20 ng/mL=229(41.5%). Mean vitamin D in African-American patients 25.7 ng/mL and non-African-American patients 32.7 ng/mL, p<0.01.

Conclusions: In comparison to others such as the DIVINE trial, we present a larger and more diverse cohort. In our study, African-Americans had a statistically significant lower vitamin D level. A case for replacing 25(OH) vitamin D even in ESKD patients is made based on the action of vitamin D beyond mineral metabolism, especially with regard to autocrine regulation of immune function. Future directions include examining effects of treatment on PTH and study of vitamin D deficient patients’ risks for adverse events like COVID-19 infection.

Prevalence of Vitamin D Deficiency in a Predominantly African-American Hemodialysis Patient Population

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Background: Vitamin D insufficiency and deficiency are common abnormalities and high risk groups include kidney disease patients and African-Americans. Recommendations on the evaluation of vitamin D levels in CKD and ESKD are ambiguous due to a lack of studies examining epidemiology and treatment. The COVID-19 pandemic has disproportionately affected minorities and has highlighted the need for evidence as studies have examined vitamin D deficiency as a risk factor for COVID-19 complications. We present a case series examining the prevalence of vitamin D deficiency in a predominantly African-American hemodialysis patient population.

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Results: Patients receiving in-center hemodialysis (n=615). Average length of time on dialysis was 5 years and average age was 59.4 years. Patients were 52.5% male(n=323), 91.5%(n=563) of patients were African-American. Mean calcium level for all patients was 8.73 mg/dL and PTH level of 554 pg/mL. Mean vitamin D in all patients was 26.32 ng/mL. 98%(n=603) of patients had a vitamin D level available. All patients with vitamin D level<30 ng/mL(412/68.3%) and all patients with vitamin D level<20 ng/mL(244/40.5%). African-American patients with a vitamin D level was 552. African-American patients with vitamin D level<30 ng/mL=382 (69.2%) and African-American patients with vitamin D level<20 ng/mL=229(41.5%). Mean vitamin D in African-American patients 25.7 ng/mL and non-African-American patients 32.7 ng/mL, p<0.01.

Conclusions: In comparison to others such as the DIVINE trial, we present a larger and more diverse cohort. In our study, African-Americans had a statistically significant lower vitamin D level. A case for replacing 25(OH) vitamin D even in ESKD patients is made based on the action of vitamin D beyond mineral metabolism, especially with regard to autocrine regulation of immune function. Future directions include examining effects of treatment on PTH and study of vitamin D deficient patients’ risks for adverse events like COVID-19 infection.

Development of a Machine Learning Approach to Management of CKD-MBD Therapy

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Background: We developed a Quantitative Systems Pharmacology (QSP) model of CKD-MBD that predicts changes in mineral metabolism. We incorporate the CKD-MBD model into an Machine Learning (ML)-based simulation to optimize the dosing of three drugs used in CKD-MBD to test the hypothesis that Reinforcement Learning (RL) approach would improve therapeutic goals.

Methods: We performed a simulated 24 month study in a virtual cohort of 80 Stage 5d CKD patients using the QSP model of CKD-MBD treated by a simulated physician (AI-Agent 0) or RL (AI-Agent 1). Agent 0 was a Deep Neural Network trained on a set of 128,061 instances. Agent 1 was developed using RL rewarding concentrations within the target range for Ca, P, PTH and avoiding Ca < 7.0 and > 10.2 mg/dL. Results of the simulation were compared using regression analysis of the dependent variable (Ca, P, PTH, calcitriol (CTL), lnFGF23, bCa(bone efflux), and vCa(vascular influx) over time with the factors RL (Agent1 vs Agent 0), P binder adherence, and equilibrium vs. steady-state. Doses of agents used to treat were compared at 24 months.

Results: Results of the statistical analysis are shown in the Table. Agent 1 using RL resulted in a greater rate of change in the dependent variables in all cases and resulted in lower model predicted concentrations of P, PTH, and FGF23 and higher concentrations.
PO0577
Role of Current Proposed Algorithm to Guide Osteoporosis Treatment in CKD: A Bone Biopsy Study

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Background: Recently, algorithms have been proposed to guide osteoporosis treatment in chronic kidney disease population. As suggested by Khararil et al., evaluation of bone turnover level by bone specific phosphate alkaline (bALP) will determine the use of anabolic or antiresorptive therapy with or without prior bone biopsy. The aim of this study is to use a cohort of CKD patients who had a bone biopsy to evaluate accuracy of this algorithm in a real-world setting.

Methods: Single-center retrospective cross-sectional study at CHU de Quebec, Canada from 2017 to 2021. CKD 4-5 patients with bone fragility and suspicion of low bone turnover or mineralization defects who had a bone biopsy were included. Results of bone biopsy were categorized based on the TMV classification. We compared the performance of the algorithm to identify potential contraindications to antiresorptive or anabolic therapy vs bone biopsy results. Receiver operating characteristic (ROC) curves were used to explore the predictive ability of bALP and tALP regarding low bone turnover and potential contraindication to antiresorptive therapy in our cohort.

Results: Twenty-six patients included (mean age 67.7 years, 11 men, 14 HD and 1 PD, 11 diabetic patients). Eleven patients had low, 8 normal and 7 high bone turnover on biopsy. According to the algorithm, no patient would have received anabolic treatment, bone biopsy would have been proposed to 10 patients and 16 would have received antiresorptive therapy. Based on the biopsy results, 8 out of these 16 patients had potential contraindications: 4 with low bone turnover and 4 with presence of mineralization defects. ROC curve for bPAl to predict low bone turnover was 0.749 (similar to tPAl). However, the AUC for tPAl to predict the presence of potential contraindication to antiresorptive therapy was lower at 0.667 (0.6095 for tPAl).

Conclusions: Algorithms using bone turnover markers can guide clinicians in approaching these patients. However, bone biopsy is still needed in many patients to better tailor anti fracture therapy until more accurate non-invasive markers are available.

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

PO0578
Different PTH Responsiveness and Bone Turnover in Japanese as Compared to European Patients Treated with Hemodialysis

Pieter Evenepoel,1,2 Hanne S. Joergensen,1,2 Hirokata Komaiba,8 Sandro Mazzarferro,2 Marc G. Vervoet,2 Etienne Cavalier,3 Masafumi Fukagawa,2 on behalf of the CKD-MBD working group of the JSN and EROD, an initiative of the CKD-MBD working group of EKTA-EDTA, Katholieke Universiteit Leuven, Leuven, Belgium; Katholieke Universiteit Leuven Universiteit Ziekenhuizen Leuven, Leuven, Belgium; Aarhus Universitetshospital, Aarhus, Denmark; Universita degli Studi di Roma La Sapienza, Rome, Italy; Universita Umberto 1 Policlinico di Roma, Roma, Italy; Universite de Liege, Liege, Belgium; Amsterdam Universitair Medisch Centra, Duivenrecht, Netherlands; Tokai Daigaku, Isehara, Japan.

Background: Parathyroid hormone (PTH) targets are lower in Japanese compared to European patients on dialysis. Whether this translates to lower bone turnover may depend on PTH responsiveness. This study tested the hypothesis that skeletal PTH responsiveness differs between Japanese and European hemodialysis patients.

Methods: Whole PTH (Roche), bone-specific alkaline phosphate (bAP, IDS-iSYS), and tartrate-resistant acid phosphatase type 5b (TRAP5b, IDS-iSYS) were centrally assessed in 378 prevalent hemodialysis patients from Japan and Belgium, matched 1:1 on age, gender, diabetes, and dialysis vintage. Patients with PTH levels at the extremes (>normal range or <15 XULN) were excluded.

Results: Patients were well matched in age (59±12 yrs), gender (66% male), diabetes (34%), and dialysis vintage (39 [22-63] months). Japanese patients had lower PTH levels (109 vs 161 pg/mL, p<0.001) and bone turnover markers (bAP 15.3 vs 24.5 μg/L, TRAP5b 3.35 vs 5.79 μL/L, p<0.001 both). Scatterplots and linear regression revealed higher bone turnover markers in European patients for any given level of PTH (Figure). In a multivariable model, Japanese nationality, male gender, higher BMI, and higher PTH were negative predictors of the TRAP5b/PTH ratio (Table).

Conclusions: Skeletal PTH responsiveness is lower in Japanese as compared to European patients on dialysis; thus, differences in PTH sensitivity cannot reconcile the current discrepancies in PTH target range.

Funding: Private Foundation Support

Table: Determinants of Ln (TRAP5b/PTH) by multivariable linear regression

Stepwise selection of variables. Model adjusted R-sq 52%, p<0.001.

PO0579
Association of Metabolic Acidosis with Impaired Bone Quality

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Background: Chronic kidney disease (CKD) is a state of impaired bone quality and strength, usually presenting as renal osteodystrophy. Metabolic acidosis (MA) is an important complication of CKD that alters bone quality and strength and is associated with increased fracture risk. Few studies have investigated bone tissue-level effects of MA in humans with CKD. We hypothesized that CKD patients with MA would have altered bone tissue-level mineral content.

Methods: This retrospective cross-sectional analysis included 22 patients with eGFR <90 mL/min/1.73m², including those receiving kidney replacement therapy, recruited from the general nephrology clinics of Columbia University Irving Medical Center. Patients were considered to have MA for serum bicarbonate <22mEq/L. Transiliac crest bone biopsy was assessed for bone formation and mineralization measures from quantitative histomorphometry of tetracycline double labels, tissue mineral density (TMD) by microCT and bone mineral density distribution (BMDD) by quantitative backscatter electron imaging (qBEl). Spearman correlations (ρ) were adjusted for eGFR. Univariate Wilcoxon tests assessed between group differences.

Results: Twelve participants had MA. There were no differences in age, sex or race/ethnicity. After eGFR adjustment, there was a correlation between serum bicarbonate and TMD (ρ =0.60, p=0.004). Bone formation and mineralization measures did not differ. TMD by microCT showed a trend. Measures of calcium content by BMDD differed between groups.

Conclusions: MA is associated with lower TMD and altered calcium content in patients with CKD. Further investigation is needed to determine whether impairments in TMD and BMDD are associated with decreased bone strength and are corrected by bicarbonate supplementation.

Funding: NIDDK Support
Impact of Urinary Calcium Excretion on Bone, Cardiovascular System, and Kidney Function in Caucasian Osteoporotic Patients: A Longitudinal Long-Term Follow-Up Study

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Background: Urinary Calcium excretion (UCaE) is expected to reflect the bone activities, however this relationship in osteoporotic (OP) patients (pts) is not well understood. Moreover, the influence of UCaE on kidney function and cardiovascular (CV) system is controversial.

Methods: Longitudinal study for OP pts who had bone biopsies between January 2008 and December 2013. All pts were white, had 24 urine collection for UCaE, DEXA scan for BMD, bone histology, and at least two follow ups with a minimum of 1-y. Exclusion criteria included active malignancies and infections, liver failure, ESKD, organ transplant, or secondary OP.

Results: Study included 118 OP pts with median follow up of 5.3 (1-11) y. The mean age was 61 ± 12 y and 89% of pts were women. The mean eGFR at baseline was 83 ± 19 mL/min. Trabecular bone volume was low in 95% of pts, 39% had high turnover bone turnover disease (HTBD) and 61% had low turnover bone disease (LTBD), while mineralization was defective in 9%. Serum calcium and 25 vitamin D were within normal range in vast majorities of pts. At baseline, lumbar spine (LS) T-score was -1.9 (-5.5 to 3.9), and total hip (TH) T-score was -1.6 (-4 to 2). Pts with HTBD had lower LS T-scores (-0.02). Hypercalcemia found in 23%. Mean UCaE was 195 ± 116 mg/d with no difference between LTBD and HTBD pts. CKD pts were older (p=0.001), had higher PTH (p=0.001), and lower UCaE (p=0.04). BMD significantly declined (>-2%) in 46% of pts at TH, and 42% at LS. BMD losers at TH were older, had lower UCaE, and lower serum albumin. Lower UCaE was significant predictor of BMD loss after adjustment of age, eGFR, and serum albumin (p=0.039, β=1.01, 95% CI (1-1.01)). Fractures occurred in 18% of pts during follow up. Fractures were higher in pts with UCaE<100. GFR declined (>3.3%/y) in 19% of pts. LTBD and HTBD pts. CKD pts had less UCaE. Lower UCaE predicted bone loss and fracture risk in white OP pts.
**Case Description:** A 59-year-old man with ESKD had longstanding well-controlled mineral bone disorder. He developed worsening hyperphosphatemia of unclear etiology, and eventually presented with symptomatic hypercalcemia with corrected calcium level of 12.9 mg/dL. Biochemistry and imaging were consistent with hypercalcemia of granulomatous lung disease. CT chest showed numerous conglomerations of centrilobular nodules in multiple lobes of both lungs (Figure 1A). Transbronchial biopsy showed giant cell granulomas containing crystalline material and calcified inclusions (Figure 1C, 1D). Infectious and rheumatological work-up was unrevealing. Detailed patient interview revealed that he had been sanding drywall without respiratory protection due to N95 mask shortage in the global pandemic. No treatment was initiated because the environmental exposure had already terminated. Over a few months, the imaging (Figure 1B) and biochemical findings resolved. A year later, the patient has well controlled mineral bone disorder on calcium-containing phosphate binders again.

**Discussion:** Our report demonstrates how systematic work-up and careful history-taking are critical in diagnosing esoteric conditions associated with hypercalcemia. It also illustrates indirect health-related effects of the coronavirus-19 pandemic on non-infected ESKD patients.

**Figure:** Case presentation of tenofovir-induced Fanconi syndrome.

**PO0585**

**An Unusual Culprit of Severe Acute Refractory Symptomatic Hypercal- cemia: Keyboard Cleaner**

**Si Yuan Khor, Nora H. Hernandez Garci1azo, Akhil Sharma, Enhua Wang, James Choi. Michigan State University, East Lansing, MI.**

**Introduction:** 1,1-Difluoroethane is commonly found in gas dusters and aerosol products. It has emerged as a recreational drug due to its acute euphoric effect. Side effects from difluoroethane abuse include hypocalcemia, acute kidney injury, cardiac arrhythmias and seizures. We report a case of 1,1-difluoroethane abuse presented with severe acute symptomatic hypercalcemia post Zoledronic acid therapy for Paget’s disease.

**Case Description:** A 35 year old male with a past medical history of Paget’s disease presented with generalized muscle cramps, facial twitching and upper extremities spasms for a day. He received IV Zoledronic acid as outpatient a day prior to the onset of symptoms. He also reported a significant history of inhalant abuse with keyboard cleaners. Physical examination were unremarkable other than a positive Trousseau sign. EKG showed prolonged QTc interval of 523 ms. Initial labs revealed corrected serum calcium 4.50 mg/dL, phosphorus 1.8 mg/dL, alkaline phosphatase 453 U/L, parathyroid hormone (PTH) 201 pg/mL, 25-Hydroxyvitamin D 7.0 ng/mL and 1,25-Dihydroxyvitamin D 146 pg/mL. Over the course of 5 days, he received a total of 24 g of IV calcium gluconate and 30 g of oral calcium carbonate. His symptoms subsequently resolved and serum corrected calcium normalized to 8.04 mg/dL and PTH decreased to 169.7 pg/mL on day 5 of hospitalization. He was discharged on day 6 with plans to follow up with primary care physician for monitoring of serum calcium level.

**Discussion:** Incidence of severe symptomatic hypercalcemia related to Zoledronic acid therapy in Paget’s disease is uncommon (1%). Our patient was treated with Zoledronic acid in the past without complication. Besides, he lacks the risk factors for bisphosphate-induced hypercalcemia which include hyperparathyroidism, hypophosphonemia and renal failure. Low 25-Hydroxyvitamin D on presentation is likely due to the effect of secondary hyperparathyroidism in response to hypocalcemia. Thus, we conclude that 1,1-difluoroethane is most likely the major precipitating factor for hypercalcemia seen in this case. Healthcare provider should be aware of uncommon causes of hypercalcemia such as difluoroethane as a differential once common causes have been ruled out, especially in certain susceptible populations given the ease of access for abuse and potentially fatal associated adverse effects.

**PO0586**

**Severe Hypercalcemia in a Patient with Acute Lobar Nephronia**

**Olesya Iliun, Martin C. Gregory, Monique E. Cho, Josephine Abraham. University of Utah Health Hospitals and Clinics, Salt Lake City, UT.**

**Introduction:** Acute lobar nephronia is a form of focal acute bacterial pyelonephritis without abscess formation or liquefaction.

**Case Description:** A 62-year-old Native American woman with a childhood history of left nephrectomy and treatment for tuberculosis was admitted for sepsis due to pyelonephritis and pan-sensitive E. coli bacteremia. Her creatinine was 5.2 mg/dL on admission, improved to 3.5 mg/dL with intravenous ceftriaxone, then increased to 4.2 mg/dL after transitioning to oral antibiotics six days later. At the same time, she developed hypercalcemia, which peaked at 13.7 mg/dL (ionized calcium 1.83 mmol/L). PTH was undetectable. Her 1,25-dihydroxyvitamin D (1,25-Vit D) was elevated at 120 pg/mL. Her serum calcium and albumin normalized, and 1,25-Vit D fell to 16 pg/mL. Her serum creatinine decreased to 2.17 mg/dL. Right kidney size decreased to 9.8 x 5.7 x 5.4 cm and had normal contour and sonographic appearance.

**Discussion:** Severe hypercalcemia is likely due to a rare pathological activation of 1α-hydroxylase (CYP27B1) in renal proximal tubule cells due to inflammatory response. Common causes of severe hypercalcemia were ruled out. Supporting this, resolution of hypercalcemia correlated with resolution of renal inflammation.

**PO0587**

**An Unusual Culprit of Acute Hypercalcemia: Keyboard Cleaner**

**An Unusual Culprit of Acute Hypercalcemia: Keyboard Cleaner**

**Wei Ling Khor, Nora H. Hernandez Garci1azo, Akhil Sharma, Enhua Wang, James Choi. Michigan State University, East Lansing, MI.**

**Introduction:** 1,1-Difluoroethane is commonly found in gas dusters and aerosol products. It has emerged as a recreational drug due to its acute euphoric effect. Side effects from difluoroethane abuse include hypocalcemia, acute kidney injury, cardiac arrhythmias and seizures. We report a case of 1,1-difluoroethane abuse presented with severe acute symptomatic hypercalcemia post Zoledronic acid therapy for Paget’s disease.

**Case Description:** A 35 year old male with a past medical history of Paget’s disease presented with generalized muscle cramps, facial twitching and upper extremities spasms for a day. He received IV Zoledronic acid as outpatient a day prior to the onset of symptoms. He also reported a significant history of inhalant abuse with keyboard cleaners. Physical examination were unremarkable other than a positive Trousseau sign. EKG showed prolonged QTc interval of 523 ms. Initial labs revealed corrected serum calcium 4.50 mg/dL, phosphorus 1.8 mg/dL, alkaline phosphatase 453 U/L, parathyroid hormone (PTH) 201 pg/mL, 25-Hydroxyvitamin D 7.0 ng/mL and 1,25-Dihydroxyvitamin D 146 pg/mL. Over the course of 5 days, he received a total of 24 g of IV calcium gluconate and 30 g of oral calcium carbonate. His symptoms subsequently resolved and serum corrected calcium normalized to 8.04 mg/dL and PTH decreased to 169.7 pg/mL on day 5 of hospitalization. He was discharged on day 6 with plans to follow up with primary care physician for monitoring of serum calcium level.

**Discussion:** Incidence of severe symptomatic hypercalcemia related to Zoledronic acid therapy in Paget’s disease is uncommon (1%). Our patient was treated with Zoledronic acid in the past without complication. Besides, he lacks the risk factors for bisphosphate-induced hypercalcemia which include hyperparathyroidism, hypophosphonemia and renal failure. Low 25-Hydroxyvitamin D on presentation is likely due to the effect of secondary hyperparathyroidism in response to hypocalcemia. Thus, we conclude that 1,1-difluoroethane is most likely the major precipitating factor for hypercalcemia seen in this case. Healthcare provider should be aware of uncommon causes of hypercalcemia such as difluoroethane as a differential once common causes have been ruled out, especially in certain susceptible populations given the ease of access for abuse and potentially fatal associated adverse effects.
Identification of Factors Affecting Changes in the Agatston Coronary Artery Calcification Score in Maintenance Hemodialysis Patients

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Background: Coronary artery calcification (CAC) has been implicated in cardiovascular disease, one of the leading causes of death in patients on maintenance hemodialysis (MHD). The Agatston CAC score is the most widely used scoring system for CAC evaluation. The factors affecting changes in the CAC score in MHD patients remain unknown. We characterized the associations between change in Agaston CAC score and clinical parameters in MHD patients.

Methods: A total of 288 patients on hemodialysis at Ichiyokai group facilities between January 2018 to February 2021 were retrospectively analyzed. Clinical parameters and Agaston CAC scores, determined by multi-detector computed tomography, were assessed at baseline and after 1 year. Patients with Agaston CAC score ≥ 30 were enrolled. A multiple regression analysis for change in Agaston CAC score was performed. The independent variables were sex, age, Agaston CAC score, glucose, albumin-corrected serum calcium, serum phosphate, β2-microglobulin, hemoglobin, blood urea nitrogen, albumin, angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) use, calcimimetic use, and vitamin D use.

Results: The mean change in Agaston CAC score was 205.2 ± 545.1 and the mean percentage change in Agaston CAC score was 21.2% ± 43.5%. The multiple regression analysis for change in Agaston CAC score identified Agaston CAC score (regression coefficient [RC] = 0.3795, p < 0.001), serum phosphate (RC = 0.1230, p = 0.0317), albumin-corrected serum calcium (RC = -0.1165, p = 0.0049), and ACE inhibitor/ARB use (RC = 0.1622, p = 0.0298) as significantly related factors (R² = 0.2011, p < 0.001).

Conclusions: In patients on MHD, change in Agaston CAC score is positively associated with Agaston CAC score and serum phosphate, and negatively associated with albumin-corrected serum calcium and ACE inhibitor/ARB use.

Qatar National Program for Screening and Management of Vascular Calcification in Hemodialysis


Background: Vascular calcification (VC) is an independent and important risk factor for cardiovascular events in (HD) patients. Trials aiming to reduce the progression of VC did not show a great success. We are presenting data from our national program for screening and management of VC in hemodialysis patients in State of Qatar.

Methods: All ambulatory HD patients in Qatar where included. Data were collected in 2020 from the Qatar national electronic medical record and it included all imaging studies (X-ray, echocardiogram, US, CT). VC then were classified into mild, moderate or severe. Patients with any VC were started on a newly created protocol to decrease calcium load (shift to non-calcium phosphate binder, reduce active vitamin D, and liberalize calcimimetic dosing). Figure 1 shows new pathway of screening and management of VC in HD patients.

Results: Total patients were 650 During the study period. 559 were screened for VC (86%) 432 (75%) had VC. We were able to classify 286 patients (67%) of them based on severity of VC on radiological findings to mild 201(70%), moderate 59(21%) or severe 26(9%). Following interventions, percentage of patients with calcium level of normal range (2.1-2.5 mmol/l) increased by 5% from 87% in March 2020 to 88% in December 2020 (p value=0.004). Phosphorus level was maintained in the range 0.81-1.8 mmol/l by 72% calcium based phosphate binder tables used weekly decreased by 30%.

Conclusions: In patients on MHD, change in Agaston CAC score is positively associated with Agaston CAC score and serum phosphate, and negatively associated with albumin-corrected serum calcium and ACE inhibitor/ARB use.
Patient’s ACC score and relationship with iPTH level

**PO0590**

Progression of Renal Osteodystrophy and Vascular Calcifications in Patients with CKD Stage II-IV

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**Background:** Vascular calcifications (VC) are associated with renal osteodystrophy (ROD) but limited data are available on ROD and VC with progression of CKD.

**Methods:** 23 pts with CKD II-IV underwent iliac crest bone biopsies for bone histomorphometry, Dual-photon absorptionmetry (DXA) of hip and spine for bone mineral density (BMD), and MScot of the aorta (AOC) and coronaries (CAC) for assessment of VC. Tests were done at baseline and after 2-3 years of observation with continuation of the same clinical management following KDIGO guidelines.

**Results:** Pts age was 60 ± 12 y with 56% female, 70% white, 26% black, 4% Asian, 57% DM II, 96% HTN, 9% CKD II, 74% CKD III, and 17% CKD IV. Results are shown in Table 1. There was an increase in VC in 5 patients and was stable in 11 pts. Pts with declining GFR had greater increases in AOC and more loss in hip BMD. AOC correlated better than CAC with BMD. At baseline there was low bone turnover (LTO) in 87% of pts, and bone volume (BV) was low in 22%. LTO decreased to 78% and low BV was increased to 45% of pts at end of study. Defective mineralization was not observed at any time.

**Conclusions:** LTO and low BV are seen in early stages of CKD. With progression of CKD, turnover increases and low BV is more frequently seen. VC are also seen early in CKD, AOCs progress faster than CACs and there is a relationship between VC and bone loss.

**Funding:** NIDDK Support, Private Foundation Support

**Table 1**

<table>
<thead>
<tr>
<th>KGF</th>
<th>TH (Bone/AOC) (mg/dL)</th>
<th>BV (Bone/BMD) (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.4 ± 1.2</td>
<td>21.8 ± 1.1</td>
</tr>
<tr>
<td>After 2-3 yrs</td>
<td>10.8 ± 1.8</td>
<td>20.9 ± 1.1</td>
</tr>
</tbody>
</table>

**PO0592**

Phosphate, Blood Pressure, and Endothelial Cell Dysfunction in a Population Study

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**Background:** Hyperphosphatemia contributes to medial vascular calcification in chronic kidney disease (CKD) patients. There is emerging evidence that phosphate (Ph) is also associated with microvascular disease in individuals with normal kidney function, with in vitro data supporting a toxic effect of Ph on endothelial cells. We hypothesized there would be an association between serum Ph, blood pressure (BP), and endothelial cell dysfunction (ECD) markers in a large, diverse cohort.

**Methods:** Using data from the Dallas Heart Study, a multi-ethnic population-based cohort, we used serum Ph as the predictor variable and conducted linear regression analysis to determine its association with systolic BP and serum asymmetric dimethylarginine (ADMA) from a single visit. We controlled for numerous demographic and clinical variables including parathyroid hormone (PTH), calcium, vitamin D, estimated glomerular filtration rate (eGFR), and albuminuria.

**Results:** There were 3301 participants with a mean age of 43 years. The median systolic BP was 122 [112, 134] mmHg. The eGFR was 102 [88, 114] mL/min. Serum calcium, Ph, PTH, and vitamin D levels were 9.2 [9, 9.5] mg/dL, 3.2 [3.2, 3.5] mg/dL, 37.3 [27, 51] pg/mL, and 17 [12, 23] ng/mL. Serum Ph and PTH were independently associated with both systolic BP and ADMA (Table 1), although there was a negative relationship between Ph and BP.

**Conclusions:** In the physiologic range, serum Ph and PTH were independently associated with higher ADMA, an ECD marker, in a diverse population while accounting for known predictors of hypertension including age, diabetes, and kidney function. Higher systolic BP was predicted by higher PTH, but lower Ph. The presence of these associations in individuals with preserved renal function warrant further studies in CKD, where hypertension and hyperphosphatemia are both more prevalent.

**Funding:** Veterans Affairs Support

**Multivariate Linear Regression Analysis**

Model also controlling for race, sex, diabetes, serum albumin, estimated glomerular filtration rate, LDL cholesterol, urinary albumin to creatinine ratio

**PO0593**

Hyperphosphatemia Is Associated with Vasoconstriction and Endothelial Cell Dysfunction in Hemodialysis Patients

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**Background:** Hyperphosphatemia is associated with increased mortality in hemodialysis (HD) patients. High phosphate (Ph) causes vascular structural changes including medial calcification. While there is in vitro evidence that high Ph can induce endothelial cell dysfunction (ECD), little is known about the relationship between Ph and vasoconstriction or ECD in HD patients.

**Methods:** Randomized, open-label, parallel-group clinical trial (control/experimental) (n=8 per group). The experimental group received 360mg of Mg carbonate daily for 15±1.5 months. At the beginning and at the end of the study, blood and urinary biomarkers of bone mineral metabolism were measured; pulse wave velocity (PWV) was determined with Mobil-O-Graph device as an indicator of arterial stiffness, the Atragato index was calculated and bone mineral density was measured by densitometry.

**Results:** The included patients were in both groups mostly men and similar with respect to age and GFR. Serum Mg concentration were 1.9±0.1 vs 2.0±0.1mg/dl in control and experimental group respectively. At the baseline, none of differences were found in demographic characteristics, comorbidities, treatments, PWV or biomarkers of bone mineral metabolism. The experimental group did not present hypermagnesemia or any other adverse event. The increase in urine Mg confirmed the therapeutic adherence. There was a decrease in GFR: 4ml/min in control and 1.7ml/min in experimental group, with no changes in serum Mg (both not statistically significant). An inverse correlation was found between urine Mg and the albumin/creatinine ratio (p=0.039). At the end of follow-up, serum Mg was inversely correlated with PWV (p=0.015). Urinary Mg was inversely correlated with iFGF23 (p=0.007). A non-significant trend of decrease in the Atragato index was observed in the experimental group. There were no changes in bone mineral density.

**Conclusions:** In CKD-4 patients the Mg supplements reduce arterial stiffness without changes in bone mineral density.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: We studied hypertensive HD patients with the following outcome data: pre-HD systolic blood pressure (BP), total peripheral resistance index (TPRI) obtained with non-invasive cardiac output monitor, and serum levels of endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA). The most recent pre-HD serum Ph was the predictor variable. We conducted correlation and multivariate linear regression analyses while controlling for other clinical variables.

Results: Among the 60 participants, the mean age was 50 years. There were 62% male, 58% Black, and 60% with diabetes. Serum Ph had significant correlations with systolic BP, TPRI, ET-1, and ADMA (Figure 1). Multivariate regression analysis showed independent associations for Ph with all outcomes except ADMA (Figure 2), but PTH did have an independent association with ADMA.

Conclusions: Hyperphosphatemia is independently associated with vasoconstriction in HD patients. Serum Ph is also associated with ECD, but this is in part confounded by PTH. These data show the adverse cardiovascular consequences of hyperphosphatemia extend beyond vascular calcification. Further human studies are needed to determine 1) if lowering Ph improves endothelial function in HD patients and 2) if pharmacologic therapy aimed at improving ECD reduces the cardiovascular burden associated with hyperphosphatemia.

Funding: NIDDK Support, Veterans Affairs Support

PO0594

Phosphate Indices and Atherosclerotic Cardiovascular Disease in CKD Patients: The CRIC Study

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Background: Phosphate (Pi) overload may induce vascular calcification and inflammation. We studied prospective association of Pi indices with ASCVD events in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: 3939 CKD patients without crosstalks were enrolled. 3096 were included in the analysis after excluding those with missing variables. ASCVD was defined as the first stroke, MI, or PAD. A new Pi burden index was calculated as [(urinary Pi/Cr ratio) x serum Pi (mg/dL) x alkaline phosphatase (ALP)] to reflect the effect of high Pi diet on kidneys, cellular space, and bones. ALP was correlated with sPi and PTH. Cox proportional hazards models were used to study associations of Pi indices with ASCVD, adjusting for ACC/AHA ASCVD and other established risk factors.

Results: Over a mean of 9 years, 699 had ASCVD events. Pi burden index was correlated with 24-hr urine Pi. FGFK23 and Pi burden index increased in early CKD. There were exposure-response associations of sPi, FGFK23 and Pi burden index with ASCVD (Table). PTH, FEPI, and 24-hr urine Pi were not associated with ASCVD.

Conclusions: Pi burden is associated with ASCVD. FGFK23 and Pi burden index increased in early CKD. They may be used for ASCVD risk classification and for monitoring phosphate overload. Future studies are warranted.
PO0596
Oral Calcitriol Use, Vertebral Fractures, and Vascular Calcifications in Hemodialysis Patients: Results from the Vitamin K Italian (VIKI) Study
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Background: Chronic Kidney Disease patients are characterized by alterations in bone and vascular metabolism associated to adverse clinical outcomes such as fractures, cardiovascular events and mortality. Dysregulation of vitamin D hormonal system, in levels of calcium, phosphate, PTH, FGF23/Klotho are the main responsible of these changes. We want to evaluate if oral calcitriol use can play a protective role on fractures in hemodialysis (HD) patients.

Methods: We included 387 HD patients of the VIKI database, a multicenter cross-sectional study. Biomarkers measured: vitamin K, VKDPs, vitamin 25(OH)D, A LP, PTH, Ca, P. Spine radiograph performed to define the presence of Vertebral Fractures (VF) and Vascular Calcification (VC). VF was indicated as ≥20% reduction of vertebral body height and VCs were quantified by measuring the length of calcium deposits along the arteries.

Results: 45.7% of patients were treated with oral calcitriol. No biochemical differences was observed between the treated and untreated patients. VFs were significantly lower in patients receiving oral calcitriol (48.6% vs 61%, P = 0.015), the presence of VCs was similar (aortic: 81.9% vs 79.5% respectively, P = 0.552; iliac: 52.0% and 59.5%, P = 0.167). In a multivariable logistic regression analysis, after adjustment for all potential confounders, oral calcitriol was associated with a marked reduction (-40.2%) of the odds of fractures (OR: 0.958, 95% CI: 0.363-0.985, P = 0.043).

Conclusions: In conclusion, we found a significant association between oral calcitriol use and lower VF rate in HD patients. Further prospective and interventional studies are needed to confirm these findings.

Funding: Private Foundation Support

PO0597
Significant Associations Between Vascular Calcification and Bone Mineral Density in CKD
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Background: Vascular calcification (VC) demonstrated as a predictor of cardiovascular mortality in chronic kidney disease (CKD) patients (pts). There are uncertainties in terms of factors that may explain the links between low bone mineral density (BMD) and mortality in CKD. We aimed to study associations between VC and BMD in CKD pts.

Methods: We studied 90 consecutive CKD pts. The following VC assessments used:
1) lateral lumbar X-rays and the scoring system to assess VC of the abdominal aorta using a semi-quantitative scoring (Kauppila,1997); 2) Ankle-brachial index (ABI) assessment (Wiskop,1950). A simple, non-invasive, accurate tool to evaluate arterial stiffness and peripheral arterial disease providing diagnostic and prognostic information with values ≥1.3 (or ≥0.9 (Ga,2019)); 3) Echocardiography; 4) BMD assessed by total body dual-energy X-ray absorptiometry (DXA).

Results: Study group pts (N=90, 41% male) median age was 64 years. Diabetes mellitus and hypertension were the common causes of CKD (29% and 28%, respectively). Kauppila score ≥1 detected in 41% of cases. The evidence of peripheral VC measured by ABI detected in 23% of cases. The heart valves calcification and fibrosis found in 41% of pts. Table demonstrates multivariate regression analysis with variables entering the equation as correlates of DXA measurements with Kauppila score and ABI as dependent variables. In pts with heart valves lesions total body BMD is significantly lower than in those who have normal heart valves. In factorial regression analysis BMD of femur, femur neck and total body BMD were significantly associated with heart valves calcification/fibrosis. BMD of femur and femur neck also inversely associated with age.

Conclusions: BMD associated with VC in pts with different CKD stages. Multi-interventional approach for diagnosis of CKD-BMD is necessary for early detection to prevent complications. Total body DXA is more informative in clinical practice for evaluation of BMD.

Funding: Government Support - Non-U.S.

PO0598
Increasing Bone Mineral Density Is Associated with Vascular Calcification in Children and Young Adults with CKD Stages 4-5 and on Dialysis
Alexander D. Lalayannis,1,2 Nicola J. Crabtree,1,2 Charles Ferro,3 David C. Wheeler,3 Neil D. Duncan,3 Colette J. Smith,3 Varvara Askiti,4 Andromachi Mitsioni,5 Lorenzo Biasioni,1 Simon Megnux,5 Kristian-El Mortensen,6 David Milford,7 Jin Long,8 Mary Fewtrell,9 Mary B. Leonard,9 Ruksheena Shoaff.1 University College London Great Ormond Street Hospital Institute of Child Health, London, United Kingdom; 2University College London, London, United Kingdom; 3Aglaia Kirakou-Geniko Nosokomeio Paidon, Athens, Greece; 4Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; 5Stanford University, Stanford, CA; 6Stanford University School of Medicine, Stanford, CA; 7University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; 8Kingston University and Children’s NHS Foundation Trust, Kingston, United Kingdom; 9University of Birmingham, Birmingham, United Kingdom; 10Imperial College Healthcare NHS Trust, London, United Kingdom.

Background: Bone mineral density(BMD) is inversely associated with coronary artery calcification(CAC) in older adults on dialysis. This association has not been shown in children and young adults where bone accrual may mitigate associations with vascular calcification.

Methods: Multicenter longitudinal study in participants aged 5 to 30 years with CKD stages 4-5 and on dialysis. Measures included tibial cortical(Cort) and trabecular(Trab) BMD by peripheral quantitative CT, CAC, carotid intima-media thickness(cIMT), pulse wave velocity(PWV) and carotid distensibility, expressed as z-scores(BMDz, cIMTz, PWVz).

Results: 98 participants (age range 13.8 ± 6.9 yrs) were assessed at baseline and 55 again after 1.5(1.3 to 1.8) years. At baseline 10% had CAC, increasing to 18% at follow-up. Median cIMTz and PWVz were 2.17(1.14, 2.86) and 1.45(-0.16, 2.57) at baseline. At follow-up cIMTz and PWVz increased, and distensibility decreased in participants with static linear growth compared to children with linear growth (Fig 1A); TrabBMDz decreased from -0.26 to -0.38, p<0.01, particularly in growing children (Fig 1B); there was a non-significant decrease in CortBMDz (0.47 to -1.13, p=0.09). On multivariable regression, baseline TrabBMDz was positively associated with cIMTz (β=0.35, p=0.001,Fig 1C). At follow-up, participants with increasing ATrabBMDz had 6-times greater odds of cIMTz increase(95% CI 1.88 to 18.35). Growing people demonstrated greater declines in TrabBMDz but less progression of vascular calcification, compared to participants with static linear growth.

Conclusions: In young people with CKD, an increase in vascular measures was seen despite an increase in BMD. Progression of vascular changes may be attenuated in the growing skeleton. Providing adequate calcium for optimal bone mineralization whilst avoiding vascular calcification remains challenging.

Fig 1. Changes in (A) vascular measures and (B) BMD in growing children vs those with static linear growth; (C) Baseline trabecular BMDz and cIMTz.

PO0599
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Assessing Efficacy of Standard and Low-Dose Hydrochlorothiazide in Recurrent Calciumre Nephrolithiasis Prevention: The NOSTONE Trial
Nasser Dhayat,1 Olivier Bonny,2 Beat Roth,2 Grazia M. Cereghetti,3 Daniel G. Fuster,1 NOSTONE investigators 'Inselstipah Universitätsklinikum Bern, Bern, Switzerland; 1Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; 2Universität Bern, Bern, Switzerland.

Background: Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8 % in men and 9.4 % in women. Without specific treatment, 5- and 10-year recurrence rates are 40% and 75%, respectively. Given the high cost of medical
treatments and surgical interventions as well as the morbidity related to symptomatic stone disease. Medical prophylaxis for stone recurrence is an attractive approach. Efficacy of thiazides for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses than used in the earlier studies. However, this practice was not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial aimed to assess the dose-response relationship of three different dosages of hydrochlorothiazide (12.5mg, 25.0mg, 50.0mg) compared to placebo in the kidney stone prevention. The primary outcome incidence of stone recurrence at 3 years is a composite of symptomatic and radiologic recurrence (comparison of basal and end-of-study low-dose CT). The study included patients from 12 hospitals throughout Switzerland.

Results: The study was approved by all competent authorities by the end of February 2017. Recruitment started in Bern on March 9th 2017. All study sites are operative since June 30th 2017. The target number of 416 patients randomized in the trial was reached on October 31st 2017 and recruitment stopped. In March 2020 the first patient randomized in the trial completed the treatment phase. All patients are expected to reach end of treatment by the end of August 2021 (www.nostone.ch).

Conclusions: The NOSTONE study will provide physicians with crucial information for the treatment of kidney stones. The impact of the results of this study will affect many patients currently under treatment with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

PO0600 Body Mass Index (BMI) and Kidney Stone Risk in Calcium Kidney Stone Formers Jie Tang,1,2 Uttam Bhetuwal,2 Brown University Warren Alpert Medical School, Providence, RI; 2Lifespan Health System, Providence, RI.

Background: The role of obesity among calcium kidney stone formers remains poorly defined, and it is unknown whether there are effect modifications of stone risk by diabetes or insulin resistance (IR).

Methods: We examined the independent associations between BMI and 24-hour urine stone risk profile among 167 calcium kidney stone formers (CSF), and analyzed the effect modifications by diabetes and IR measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in non-diabetics. Study participants were recruited from Lifespan Kidney Stone Clinic. We used linear regression and adjusted for demographics.

Results: The study population (n=167) had a mean age of 53 years, 77 (46%) were male, and 135 (81%) had diabetes. Mean BMI was 29 (Interquartile range: 25 to 33). Higher BMI was associated strongly with diabetes (p<0.0001). Among 159 non-diabetic CSFs, mean BMI was 28 (IQR 25 to 31), and BMI had a strong positive association with HOMA-IR (p<0.001). 33% of non-diabetic CSFs had hypertension (vs. 100% in diabetics), 21% of non-diabetic CSFs had dyslipidemia (vs. 89% in diabetics). HOMA-IR ranged from 0.42 to 28.2 (mean 4.3). Overall, in the whole study population, BMI had significant positive associations with urine ammonium, uric acid (UUA), and UUA supersaturation (p<0.004, <0.0001, <0.0001 respectively).

The strong association between BMI and uric acid was only observed among diabetics (p=0.006), with a similar trend observed among non-diabetics with high IR (p=0.09 when HOMA-IR>10, p=0.09 when HOMA-IR=5−10, p=0.02 when HOMA-IR<5).

On the contrary, the uricorific effect of higher BMI was only observed in nonobdietics who had normal or near-normal IR (p=0.3 among diabetics, p<0.0001 when HOMA-IR<5, p=0.05 when HOMA-IR<10). As a result, BMI and UUA supersaturation tended to have weak associations with BMI among diabetics or non-diabetics who had high IR (p=0.09 in diabetics and those with HOMA-IR>10, p=0.2 when HOMA-IR>5). Lastly, BMI did not have significant associations with serum levels of vitamin D and uric acid, plasma parathyroid hormone concentration and measurements of other urinary stone risk factors.

Conclusions: In our cohort of CSFs, higher BMI had strong associations with urinary uric acid and ammonium excretions, and these associations appeared to be modified by the presence of diabetes or IR.

Funding: Clinical Revenue Support

PO0601 Examining the Clinical Effectiveness of Calcium Oxalate Stone Treatments Joseph T. Gutbroad, Charles C. Keys McKay, Elaine M. Worcester, Megan Prochaska. 1and 2 are co-first authors University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: Lowering urine calcium oxalate (CaOx) supersaturation (SS) is a primary clinical focus for CaOx kidney stone (KS) prevention and can be achieved by increasing urine volume, or decreasing urine calcium or oxalate excretions. Common clinical strategies for this include advising patients to increase fluid intake, restrict dietary sodium, restrict dietary oxalate, or prescribing a thiazide-type diuretic. Several of these strategies have been validated in the controlled setting of randomized trials but efficacy in the real-world clinical setting is less clear. We investigated the efficacy of these treatment strategies in a clinical setting, observing whether trial-based findings on CaOx KS treatment hold true.

Funding: Clinical Revenue Support

PO0602 Effect of Hydroxycitrrate (HCA) on Urine Chemistry in Calcium Kidney Stone Formers David S. Goldfarb,1,2 Kumar Rohit,1 Avinash G. Adiga,3 Briony L. Norris,4 Lee Yang,3 Frank Modersitzki,1 David A. Bushinsky,3 Jeffrey D. Rimer,3 John R. Asplin,3 1NYU Langone Health, New York, NY; 2LithoLink Corp, Chicago, IL; 3University of Rochester Medical Center, Rochester, NY; 4University of Houston, Houston, TX; 5Salem Health, Salem, OR; 6The Royal Melbourne Hospital, Melbourne, VIC, Australia; 7University of Alabama, Tuscaloosa, AL.

Background: Potassium citrate is a mainstay of treatment to prevent recurrent calcium-containing kidney stones. However, it can increase urine pH and calcium phosphate (CaP) supersaturation (SS), HCA, extracted from Garcinia cambogia, is a potent inhibitor of calcium oxalate crystal growth in vitro and should not provide "potential base", as citrate does. Effect of HCA has not been well-studied.

Methods: We enrolled 2 groups: calcium stone formers (SF, n = 9) and non-stone forming (NSF, n = 9) controls (after excluding 2 SF and 2 NSF whose urine creatinine excretion on the 2 collections differed by more than 20%). Mean age 49.3 years. Thiazides and citrate were held for 2 weeks prior to study. Participants recorded a self-selected diet for 2 days and performed 24-hour urine collection on day 2. HCA was purchased online from Amazon.com (Super CitriMax Garcinia Cambogia); 2 caps = 900 mg of HCA. Participants took 900 mg 3 times daily orally for 7 days. Diet from days 1 and 2 was replaced with day 6 and 7 of the HCA arm of the study. 24-hour urine was collected on day 7. Urine was sent to Litholink, Inc. (Chicago, IL) for analysis. Urinary excretion of hydroxycitrate and citrate were measured using LC/MS.

Results: According to label, 6 pills would provide 2700 mg (13.2 mmol) of HCA per day, we measured content in 3198 mg (15.6 mmol). Citrate content is supposed to be 0, but we found 126 mg (0.66 mmol) per day. Both NSF and SF had appearance of HCA in the urine: 1.86 ± 0.80 and 2.07 ± 0.67 mmol/day (p = 0.56). Urine chemistry seen in Table 1. In NSF, pH and citrate did not change. In SF, pH increased, citrate did not. K went down in both groups.

Conclusions: Administration of HCA, a potential inhibitor of Ca stone formation, leads to significant urinary HCA excretion. Citrate excretion was not affected. Urine pH increased, suggesting some alkalizing effect. The difference in NSF and SF may be due to the lowering start pH in SF. The effect of HCA on stone formation remains to be determined.

Funding: Clinical Revenue Support

Urinary chemistry after HCA

<table>
<thead>
<tr>
<th>Baseline NSF</th>
<th>Baseline SF</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>6.67 ± 0.62</td>
<td>6.63 ± 0.58</td>
</tr>
<tr>
<td>Citrate (mmol)</td>
<td>687 ± 196</td>
<td>687 ± 193</td>
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Background: There have been no trials examining efficacy of interventions aimed at decreasing stone risk in patients with EH. We drew upon data in patients in a kidney stone clinic, using consistent methodologies over time. We asked how doctors made therapeutic choices and which therapies were effective at decreasing stone risk.

Methods: We selected 100 patients with EH from the Kidney Stone Evaluation and Treatment Program at the University of Chicago between 1970 and 2018. We analyzed 24-hour urine collections before and after patients’ first clinical visit using multivariate linear regression and t-tests to compare effects of fluid intake and oxalate-focused interventions on outcomes.

Results: Compared to those who did not receive the advice, advice to increase fluid intake resulted in a larger pre- to post-advice increase in urine volume (0.6 vs. 0.09L/day, p<0.001) and decrease in CaOx SS (-3 vs. -1, p<0.001). Compared with those who did not receive the advice, advice to restrict dietary sodium alone resulted in a larger pre- to post-advice decrease in urine sodium (-28 vs 13mg/day, p=0.002) but there was no change in urine calcium or CaOx SS without concurrent thiazide. Thiazide prescription resulted in a significant pre- to post-advice decrease in urine calcium for patients who also sodium restricted (-69mg/day, p<0.001) and those who did not sodium restrict (-55mg/day, p<0.001) with a trend towards a larger decrease in those who did both (p=0.06). Thiazide prescription resulted in a significant pre- to post-advice decrease in urine CaOx SS for patients who also sodium restricted (-3, p<0.001) and those who did not (-2, p<0.001).

Conclusions: In a real-world clinical setting, advice to increase fluid intake fluid or a thiazide diuretic prescription and reduction in sodium intake lowered CaOx SS and CaOx KS risk in follow up.

Funding: NIDDK Support
PO0604
High Oxalate Concentrations Increase Risk for Sudden Cardiac Death in Dialysis Patients
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Background: The clinical significance of accumulating toxic terminal metabolites such as oxalate in kidney failure patients is imperfectly defined. Our study evaluated whether oxalate concentrations are associated with risk of all-cause mortality and cardiovascular events in a cohort of patients with kidney failure requiring chronic dialysis.

Methods: To relate all-cause death and cardiovascular events to serum oxalate, we performed a post hoc analysis of a randomized controlled trial conducted between March 1998 and October 2002 that comprised 1255 European hemodialysis patients with diabetes who were followed up for a median of 4 years (4D Study). The results obtained via Cox proportional hazards models were confirmed by competing risk regression and restricted cubic spline modeling in the 4D cohort, and validated in a separate cohort of 104 US dialysis patients after a median follow-up of 2.5 years.

Results: A total of 1108 patients with a mean (SD) age of 66.3 (8.3) years had baseline oxalate measurements with a median (IQR) oxalate concentration of 42.4 (30) micromolar. During follow-up, 548 patients died, including 139 (25.4%) patients who died from sudden cardiac death. A total of 413 patients reached the primary composite cardiovascular endpoint, which comprised cardiac death, nonfatal myocardial infarction, or fatal or nonfatal stroke. Participants in the highest oxalate quartile (above 59.7 micromolar) had a 40% increased risk for cardiovascular events (HR per doubling, 1.40; 95% CI 1.18-1.81) and a 62% increased risk of sudden cardiac death (adjusted HR 1.62; 95% CI 1.03-2.56), compared to patients in the lowest quartile (below 29.6 micromolar). The associations remained when accounting for competing risks, and with oxalate as a continuous variable, and could be reproduced in a separate cohort of 104 US dialysis patients.

Conclusions: Elevated oxalate concentrations are a novel risk factor for cardiovascular events and sudden cardiac death in dialysis patients. Further research is required to determine the role of oxalate in vascular calcification and cardiovascular disease in kidney failure.

Funding: NIDDK Support

PO0605
Association of Serum Sclerostin Levels with Mortality in Maintenance Hemodialysis Patients: An 8-Year Prospective Cohort Study
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Background: Sclerostin is an osteocyte-derived inhibitor of bone formation and is increased in kidney failure. Sclerostin might be involved in the pathogenesis of vascular calcification and cardiovascular disease, but few studies examined the association between sclerostin and mortality in hemodialysis patients.

Methods: We analyzed a cohort of 654 maintenance hemodialysis patients enrolled in the Tokai Dialysis Prospective Cohort Study. The primary exposure variable was the baseline serum sclerostin level, measured using a sandwich ELISA (Bioendex Medizinprodukte GmbH & Co KG). The primary outcome was 8-year all-cause mortality. Mortality risk was assessed using Cox regression models adjusted for potential confounders.

Results: Baseline median (IQR) sclerostin level was 163 (120-215) pmol/L. Patients with higher sclerostin levels were likely to be male, have diabetes, have better nutritional status, higher hemoglobin, and lower intact PTH and bone turnover markers. No associations were observed between serum sclerostin and cardiovascular comorbidities. During a median follow-up of 7.6 years (IQR, 4.1-8.0 years), 229 of the 654 participants died. In univariate analysis, serum sclerostin levels were not associated with mortality (HR per doubling, 0.94; 95% CI, 0.76-1.17). This result was unchanged after adjustment for age, sex, dialysis vintage, diabetes, prior cardiovascular disease, body mass index, hemoglobin, albumin, and creatinine (HR per doubling, 1.07; 95% CI, 0.82-1.40).

Conclusions: Serum sclerostin levels were not associated with mortality in maintenance hemodialysis patients. Further research is required to determine the role of sclerostin in vascular calcification and cardiovascular disease in kidney failure.

Funding: Government Support - Non-U.S.

PO0606
Association Between 24-Hour Urine Sodium or Potassium Excretion and Cardiovascular Events in Veterans with Urinary Stone Disease

Background: Urinary stone disease (USD) is associated with an increased risk of major adverse cardiovascular events. Recent studies that estimated 24-hour urine excretion from spot urine samples have demonstrated an association between high urine sodium excretion and low urine potassium excretion are independently associated with cardiovascular events. Since patients with USD undergo 24-hour urine testing for stone prevention, direct 24-hour urine testing for sodium and potassium excretion may provide insight into cardiovascular risk for patients with USD.

Methods: We identified 6,401 Veterans with USD and a 24-hour urine sodium measurement and 4,950 Veterans with USD and a 24-hour urine potassium measurement between 2007 and 2015 from national VA data. We defined the primary outcome as an inpatient or emergency department diagnosis of acute myocardial infarction, unstable angina or stroke or a procedural code for percutaneous coronary intervention or coronary artery bypass graft surgery. We performed Cox proportional hazards regression to identify the risk of a cardiovascular event by level of 24-hour urine sodium and or potassium excretion.

Results: Among the 6,401 Veterans with USD and a 24-hour urine sodium measurement, 715 (11.2%) had a major cardiovascular event. Veterans with a 24-hour urine sodium in the lowest 10th percentile (~113 mEq/l) had a higher risk of a cardiovascular event compared to those with a 24-hour urine sodium between the 11th and 90th percentiles (HR 1.55, CI 1.25-1.92). We found no significant association between 24-hour urine potassium excretion and cardiovascular events.

Conclusions: Patients with lower 24-hour urine sodium excretion have a higher risk for cardiovascular events. Patients with higher 24-hour urine sodium or potassium excretion or lower 24-hour urine sodium or potassium excretion do not have a higher risk of cardiovascular events. These findings differ prior studies that used spot urine samples to identify patients who are at risk for cardiovascular disease, suggesting that direct measurement of 24-hour urine sodium or potassium excretion more accurately identifies patients who are at risk for cardiovascular disease.

PO0607
Indoxyl and Cresyl Sulfate Are Respectively Linked to Phosphoclastic Metabolism Abnormalities and to Cardiovascular Morbidity in Hemodialysed Patients
Arianna Bolonga, Giuseppe Vezzoli, Nadia Edvige Foligno, Monica Avino, Teresa Del Mastro, Teresa Arcidiacono. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Indoxyl sulfate (IS) and Cresyl sulfate (CS) are uremic toxins generated by the intestinal amino acid catabolism. Blood levels of these toxins increase in patients with CKD and are linked to cardiovascular events.

Methods: Therefore, we studied the relationship between serum levels of free IS and CS and prevalent ion metabolism variables and cardiovascular and cerebrovascular outcomes (stroke, heart failure, angina and myocardial infarction) in 139 hemodialysis patients (age 68±13 years, weight 65±13 kg, dialysis vintage 69±71 months). We divided patients according to tertiles of free serum IS and CS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0608
Expression Pattern of the Runt-Related Transcription Factor (RUNX) Family and the Role of RUNX1 During Kidney Development
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Background: RUNX family plays critical roles during the developmental process in multiple organs. The mammalian RUNX family consists of RUNX1, RUNX2 and RUNX3, each of them has distinct tissue-specific expression and function but also has a redundancy. Here, we examined the distribution of RUNX family in the kidney. We also assessed the involvement of RUNX1 during renal development in the conditional knockout mice using Cre-LoxP strategy.

Methods: We examined the temporal and spatial expression pattern of RUNX family in the kidney by immunostaining and qPCR analysis. To analyze the role of RUNX1 in kidney development, we utilized HoxB7-Cre mice and R26CreERT2 mice. To induce activation of CreERT2, we administered tamoxifen to pregnant mothers at E12.5 and analyzed the embryos at E16.5. Long-term observation was impossible due to the severe anemia caused by hematological toxicity of the systemic activation of CreERT2.

Results: In the neonatal kidney, RUNX1 was strongly expressed in the uretic bud (UB) tip and also weakly expressed in the distal portion of renal vesicle, comma body, and S shaped body. RUNX1 was also expressed in the pelvic urethelium and immune cells. RUNX1 expression in the UB tips was detectable from E13.5 and disappeared by P7. In contrast, RUNX2 was restricted in the stroma firstly detected from E15.5 and was strongly expressed in both cortical and medullary fibroblasts at P2. RUNX3 was only expressed in the immune cells. There was no difference in the number of UB branching or Six2+ nephron progenitor cells per UB tip in Runx1+/+ or HoxB7-Cre mice, which lack Runx1 expression in UB. Further analysis utilizing Runx1dr1: R26CreERT2 mice showed no obvious abnormality. In addition, neither RUNX2 nor RUNX3 compensated the loss of RUNX1 in deficient embryos.

Conclusions: We precisely analyzed the unique expression pattern of RUNX family during kidney development and identified RUNX1 as the marker of UB tip and RUNX2 as the marker of fibroblasts in the embryonic kidneys, although RUNX1 was dispensable for nephrogenesis.
activity upon β-catenin stabilization, while mutated-Tcf21 failed to increase TCF/LEF activity. A transgenic immunoprecipitation assay showed that Tcf21 is bound to β-catenin at basal and activated states in vitro.

**Conclusions:** Together, our findings suggest that Stroma-Tcf21 is essential for medulary stroma development, by enhancing Wnt/β-catenin signaling to promote stromal cell proliferation and differentiation. Stromal Tc21 is also required for the development of the adjacent nephron epithelia.

**Funding:** NIDDK Support

**PO0611**

**ZEB2 Is Essential for FOXD1+ Kidney Stromal Progenitor Cell Differentiation During Kidney Development**

Sudhir Kumar, Xueming Fan, Hila Milo Rasouly, Richa Sharma, David J. Salant, Weining Lu. *Boston University School of Medicine, Boston, MA.*

**Background:** FOXD1+ derived stromal cells are essential for normal kidney development. They give rise to pericytes and resident fibroblasts that support the kidney vasculature and also cooperate with cells that give rise to the developing nephron. However, FOXD1+ derived stromal progenitors may also serve as precursors of myofibroblasts in kidney fibrosis. The signals that regulate the differentiation of FOXD1+ stromal progenitors are not well understood. Given that zinc finger E-box-binding homeobox2 (ZEB2), a SMAD-interacting transcription factor, is expressed in developing kidney stromal cells, we examined the role of ZEB2 in kidney stromal cell differentiation in the developing mouse kidney.

**Methods:** We generated Zeb2 conditional-specific knockout mice (cKO) by crossing Zeb2flx/flox mice with Flk1Cre/Cre mice and analyzed the phenotype of homozygous Zeb2flx/−;Flk1Cre/Cre mice (Zeb2 cKO) and their wild-type littermate controls. Kidney histology and cell proliferation function were examined in Zeb2flx/flox mice. Cell fate mapping was performed using tdTomato mice. Protein expression analyses were performed by immunostaining and Western blotting of several markers for stromal progenitors, pericytes, fibroblasts, myofibroblasts, endothelial cells, renal tubules, and SMAD proteins in Zeb2 flx/flx and wild-type controls. Nephrogenesis was analyzed by immunostaining using nephron morphogenesis markers SIX2, WT1, nephrin, and Jagged1.

**Results:** Deletion of mouse Zeb2 in FOXD1+ stromal progenitors produced dysplastic and hypovascular kidneys. The Zeb2 deficient FOXD1+ stromal progenitors in these kidneys took on a myofibroblast cell fate that led to kidney fibrosis and kidney failure. Cell marker studies confirmed that these myofibroblasts expressed pericyte and resident fibroblast markers including PDGFRα, CSPG4, Desmin, GLI1, and NTSE. Notably, increased interstitial collagen deposition associated with loss of Zeb2 in FOXD1+ stromal progenitors was accompanied by increased expression of activated SMAD1/5/8, SMAD2/3, and SMAD4.

**Conclusions:** Our study identifies a key role of ZEB2 in maintaining the cell fate of FOXD1+ stromal progenitors during kidney development and loss of ZEB2 leads to differentiation of FOXD1+ stromal progenitors into myofibroblasts and kidney fibrosis.

**Funding:** NIDDK Support

**PO0612**

**Uncovering the Podocyte Foot Process Proteome**

Gary F. Gerlach, Lori L. O’Brien. *University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.*

**Background:** Podocyte foot process integrity is vital for kidney function and health. Disruptions to podocyte architecture, or effacement, is one of the most common observations in kidney disease. However, the full complement of players responsible for podocyte foot process integrity is still unknown. The membranous cellular environment and specialized junctional complexes have previously hindered their isolation and testing.

**Methods:** The discovery of a proximity-dependent biotin identification (BioID) moiety that utilizes a promiscuous biotin ligase has opened new avenues to generate spatially localized proteomes. Podocin-BioID2 localizes to the slit diaphragm and is one of the most abundant foot process proteins. Therefore, we developed a novel genetic mouse model via knock in of the BioID moiety to the Nps2 locus (podocin-BioID2) to identify the in vivo proteome of the podocyte foot process localized within the vicinity of podocin.

**Results:** We validated our transgenic podocin-BioID2 model by assessing correct expression and localization of the fusion protein via western blot, immunofluorescence (IF), and electron microscopy (EM). Injection of podocin-BioID2 mice with excess biotin leads to the significant biotinylation of proteins within podocytes. We isolated the biotylated proteins and performed mass spectral analyses (MS) to uncover novel proteins localized to the foot process. In silico analysis of the top proteins uncovered the prominent moiety that utilizes a promiscuous biotin ligase has opened new avenues to generate spatially localized proteomes. Podocin (Nps2) is one of the most abundant foot process proteins. Therefore, we developed a novel genetic mouse model via knock in of the BioID moiety to the Nps2 locus (podocin-BioID2) to identify the in vivo proteome of the podocyte foot process localized within the vicinity of podocin.

**Conclusions:** We validated our transgenic podocin-BioID2 model by assessing correct expression and localization of the fusion protein via western blot, immunofluorescence (IF), and electron microscopy (EM). Injection of podocin-BioID2 mice with excess biotin leads to the significant biotinylation of proteins within podocytes. We isolated the biotylated proteins and performed mass spectral analyses (MS) to uncover novel proteins localized to the foot process. In silico analysis of the top proteins uncovered the prominent moiety that utilizes a promiscuous biotin ligase has opened new avenues to generate spatially localized proteomes. Podocin (Nps2) is one of the most abundant foot process proteins. Therefore, we developed a novel genetic mouse model via knock in of the BioID moiety to the Nps2 locus (podocin-BioID2) to identify the in vivo proteome of the podocyte foot process localized within the vicinity of podocin.

**Funding:** NIDDK Support

**PO0613**

**Autophagy Deficiency in Urothelial Cells Activates Progressive NF-κB Signaling**

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**Background:** The urothelium is a specialized epithelium that functions as a urine permeability barrier along the upper urinary tract and bladder. We have shown that conditional knockout (CKO) of exocyst gene Exo5 in ureretic bud cells disrupts the urothelial stratification process during ureter development, which subsequently triggers cell death and ureter obstructions. This Exo5 CKO mouse is a novel model of congenital obstructive uropathy (COU) and may be useful for elucidating the underlying pathological mechanisms of COU. Here, we investigated the role of exocyst-mediated autophagy in the stress responses of urethelial cells.

**Methods:** Cre/loxP Exo5+ urothelial ablation was accomplished with Ksp-Cre and Ucp3-Cre;Exo5fl/fl mouse driver strains for both embryonic and adult urothelial knockout. An immortalized human urothelial cell line (SV-HUC-1) was used for cellular assays. Autophagic flux and cell stress signaling were measured by immunofluorescence and western blotting.

**Results:** We report that urethelial Exo5 ablation disrupted autophagy and promoted non-canonical NF-κB signaling during ureter development in Ksp-Cre mice. Adult urothelial Exo5-knockout mice also showed disrupted autophagy, with an accumulation of lysosomes in the bladder urothelium. In SV-HUC-1 cells, EXO4 co-immunoprecipitated with ATG7, and silencing of Exo5 led to an accumulation of LC3II/I and p62, indicating poor autophagic flux. Direct inhibition of autophagy with BafA1 or VPS34 induced an early canonical RelA NF-κB response followed by a delayed p52 non-canonical NF-κB response and eventual cell death.

**Conclusions:** Here, we report that Exo5 contributes to autophagy in urethelial cells, and impaired autophagy triggers progressive NF-κB signaling. The initial stress response activates canonical RelA NF-κB signaling, which is associated with survival mechanisms and inflammation. However, when the injury is not resolved, a delayed p52 non-canonical NF-κB signaling follows. Under these conditions, the non-canonical NF-κB mediators TWEAK and its receptor Fn14 were highly responsive. Further investigation of this progressive NF-κB signaling series in urethelial cells may be critical for understanding the etiology of COU and any lingering chronic response after COU is resolved.

**Funding:** NIDDK Support

**PO0614**

**Mechanisms of VEGFR3 Signaling in Glomerular Development**

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**Background:** Dysregulation of Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), known primarily for its role in lymphangiogenesis, is causally linked to the development of kidney diseases, including renal fibrosis and cystogenesis. However, the mechanisms of VEGFR3 signaling in kidney development, how it influences kidney disease, and the vascular beds involved remains uncertain.

**Methods:** We performed a detailed expression profile of VEGFR3 in the developing mouse kidney from embryonic age E13.5 through 3 months. We generated a new transgenic mouse model to investigate the role of Vegfr3 in the kidney vasculature (Vegfr3GFP). Conditional and cell-specific excision of the floxed allele was performed using the Rosa26R-TetO-Cre, Cdh5-Cre;ERT2, and Prox1-Cre;ERT2 driver strains to evaluate global, pan-endothelial, and lymphatic endothelial cell deletion of Vegfr3 respectively. Additionally, breeding of mice carrying podocyte-specific deletion and overexpression of the VEGFR3 ligand, VEGF-C, are underway to define ligand-dependent and independent function of VEGFR3 in the glomerulus. Mice underwent a detailed phenotypic evaluation and kidney sections were processed for histology.

**Results:** VEGFR3 undergoes dynamic expression through development in glomerular endothelial cells (GECs), beginning with high expression in the angiogenic sprouts which invade the capillary cleft of the developing nephron. Constitutive deletion of Vegfr3 during mid-embryonic development resulted in reduced viability, lymphatic vascular defects, a reduction in kidney size, and a reduction in average cross-sectional glomerular count on serial sectioning (mean difference = -3.767 ± 1.238, p <0.005). Additionally, deletion of Vegfr3 at embryonic day 11.5 demonstrated marked disruption of glomerular development with cavernous capillary malformations. Immunofluorescence and electron microscopy revealed glomerular structures surrounded by simplified podocytes, abnormal attachment of endothelial cells with reduced fenestrations, and poor formation of the glomerular basement membrane. VEGF-C mutant mice will be characterized once available.

**Conclusions:** VEGFR3 is expressed in GECs and is integral to normal glomerular development. The mechanisms of VEGFR3 signaling in GEC crosstalk with podocytes will be essential to determine prior to the development of therapeutics targeting this pathway.

**Funding:** NIDDK Support, Private Foundation Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PO0615

The ATP-Binding Cassette Protein ABCG2 Marks Kidney Resident Endothelial Colony-Forming Activity in Multiple Endothelial Clusters Identified by Single-Cell RNA Sequencing

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Background: Side-population cells (SP) were originally identified in hematopoietic stem cells based on their ability to efflux the DNA binding dye Hoechst 33342, an activity thought to be mediated by members of the ATP-binding cassette protein family such as ABCG2. We hypothesized that ABCG2-expressing endothelial (EC) cells are enriched in colony forming cell (ECFC) activity, and may contribute to vascular homeostasis in kidney.

Methods: The fate of ABCG2 expressing EC was investigated using adult Babg2-CreERT X Td-tomato Rosa26 reporter mice (ABCG2-2T). Transgene with tamoxifen (TMX; 50 µg/g, 1X) followed by FACS analysis for TdTomato in EC. For single-cell RNA sequencing, mouse kidney ECs were isolated following digestion with collagenase, and CD45 depleted/CD31(positive) magnetic selection. Isolated single cells were sequenced using the 10X platform. Data were analyzed with Seurat.

Results: 24 hours following TMX, 2.9% of kidney EC (CD31+ /CD45−) expressed TdTomato. The percentage of Td-Tomato+ EC progressively increased to 5.3% (p<0.4) by 1 week and 15.4% (p<0.001) by 6 weeks post-injection. To determine the EC subtypes expressing ABCG2-associated progenitor activity, scRNAseq was conducted on isolated kidney endothelial cells of ABCG2-2T mice 24 hours following TMX injection. A total of 10 endothelial clusters were identified. Analysis of top expression genes suggested these clusters correspond to different kidney EC populations such as peritubular capillaries, venules, arteries, arterioles, AVR, DVR and lymphatics. The expression of the reporter was based on identification of WPRE response element expressed Rosa mice following Cre activation. Interestingly, no single discrete cluster of ECs expressing WPRE were identified. Rather, a variable percentage (4.3 to 38.7%) of WPRE expressing cells were identified in each cluster.

Conclusions: Taken together these data suggest that ABCG2+ expressing cells contribute to vascular maintenance in adult kidney and that such cells are found in most kidney EC populations. In addition, reporter expressing EC cells do not represent a transcriptionally distinct subset of EC but are transcriptionally similar to the surrounding tissue endothelial cell subsets.

Funding: NIDDK Support

PO0616

Stromal-Derived Ntn1 Influences Renal Vascular Formation and Kidney Development

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Background: Renal vascular networks are critical to maintain fluid homeostasis. Despite their important roles, formation and patterning of the renal endothelium and its effect on kidney development are poorly understood. Netrin-1 (Ntn1) is a secreted ligand critical for vascular guidance during embryogenesis and is highly expressed by renal stromal progenitors (SP). Therefore, ntn1 is an ideal candidate for regulating endothelial cell (EC) activation and migration.

Methods: To investigate the role of netrin signaling during kidney development, we deleted Ntn1 from SPs and interrogated the embryonic phenotype using immunofluorescence, high-resolution and 3D microscopy, and cellular analyses.

Results: Conditional knock-out (cKO) of Ntn1 results in hypoplastic kidneys, extended nephrogenesis, and arterial mis-patterning. Using 3D light-sheet microscopy, we observed that netrin signaling is crucial for vascular guidance during embryogenesis and is highly expressed by renal stromal progenitors (SP). Therefore, netrin-1 is an ideal candidate for regulating vascular formation and premature emergence of neighboring lateral vessel progenitors (LVPs). Kidney progenitors originate within the intermediate mesoderm (IM), but the pathways that establish the boundary between the IM and its neighboring vessel progenitors are poorly understood.

Conclusions: We employ a combination of loss-of-function and gain-of-function genetics, RNA in situ hybridization, immunohistochemistry, and transgenesis in the zebrafish model system.

Funding: NIDDK Support, Private Foundation Support

PO0617

Three-Dimensional Visualization of Neonatal Glomerulogenesis in the PodoTRAP Model by Simplified Tissue-Clearing Approach

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Background: The process of glomerulogenesis is complex and the dynamics and spatio-temporal coordination involved in the formation of the glomerular architecture are poorly understood. Conventional histopathological methods and 2D-microscopy techniques allow only a limited visualization and reconstruction of processes in the developing kidney which can only be fully appreciated in a 3-dimensional context.

Methods: To specifically study the organisation, maturation and arrangement of podocyte during glomerulogenesis, we used neonatal kidneys from PodoTRAP transgenic animals (P0, P3, P7) in combination with a modified ethyl cineamate (EC)-based clearing approach for immunostaining and subsequent 2-photon microscopy. We used IMaris for comprehensive morphometric analysis and 3D-reconstruction of podocytes and glomeruli during postnatal kidney development.

Results: Tissue clearing is a technique to render biological samples transparent, thereby allowing for high resolution 3D-microscopic imaging of structures deep within the tissue without the need for conventional tissue-sectioning. We used this technique for 3D-imaging, reconstruction and analysis of different glomerular developmental stages (renal vesicles, 5-phase, capillary loop, maturing glomerulus) in transparent kidneys of P0, P3, P7 as well as adult PodoTRAP mice. E-clearing followed by 2-photon microscopy achieved significantly higher imaging depth compared to uncleared kidneys (~100µm vs. ~150µm). GFP podocytes in E-cleared PodoTRAP kidneys were readily identified due to robust cellular epifluorescence, with GFP signal intensities increasing as podocyte maturation progressed. Amongst others, we conducted comprehensive quantification of glomerular volume increases during postnatal kidney development.

Conclusions: The combination of E-cleaning and 2-photon microscopy in the PodoTRAP model is well suited for high-resolution 3D-imaging of renal tissue including detailed morphometry of maturing glomeruli in whole neonatal mouse kidneys. Moreover, this approach could also be useful for holistic histopathological analyses and assessments in various glomerular disease models including FSGS.

Funding: NIDDK Support, Other NIH Support - 5T32HL069768

PO0618

OSR1 Couples Intermediate Mesoderm Cell Fate with Temporal Dynamics of Vessel Progenitor Cell Differentiation

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Background: Transcriptional regulatory networks refine gene expression boundaries throughout embryonic development to define the precise dimensions of organ progenitor territories. Kidney progenitors originate within the intermediate mesoderm (IM), but the pathways that establish the boundary between the IM and its neighboring vessel progenitors are poorly understood.

Methods: We employ a combination of loss-of-function and gain-of-function genetics, RNA in situ hybridization, immunohistochemistry, and transgenesis in the zebrafish model system.

Results: Here, we delineate new roles for the zinc finger transcription factor Osr1 in kidney and vessel progenitor development. Zebrafish osr1 mutants display decreased IM formation and premature emergence of neighboring lateral vessel progenitors (LVPs). These phenotypes contrast with the increased IM and absent LVPs observed with loss of the bHLH transcription factor Hand2, and loss of hand2 partially suppresses the osr1 mutant phenotypes. hand2 and osr1 are both expressed in the posterior lateral mesoderm, but hand2 expression decreases dramatically prior to LVP emergence. Induction of osr1 expression after gastrulation is sufficient for inhibiting LVP development and rescuing IM and pronephron formation.

Conclusions: Together, our data demonstrate that osr1 modulates both the extent of IM formation and the temporal dynamics of LVP development, suggesting that a balance between levels of osr1 and hand2 expression is essential to demarcate the dimensions of kidney and vessel progenitor territories.

Funding: NIDDK Support, Private Foundation Support

PO0619

Membrane Phosphoinositides and Renal Epithelial Cell Polarity Determination in the Xenopus Prenephros In Vivo

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Background: Though only minor components of cell membranes, phosphoinositide lipids (PIs) participate in numerous signaling processes and in membrane identity determination. Many studies of cationic PI (cPI) cell membrane distribution have identified PIs as distributed with polarity among plasma membrane (PM) domains, and that their polarized distributions are required for the delivery of distinct populations of apical and basolateral membrane proteins. The extent to which PIs drive these processes in actual renal epithelial cells in vivo has never been examined for the Prenephros of Xenopus Tropicaalis tadpoles using MCherry-tagged Pleckstrin Homology (PH) domains that selectively bind different PIs (PH-AKT, PH-PLCδ1, which bind to (PI(3,4,5)P3 and PI(3,4,5)P2 respectively) with the goal of assessing whether and how PI localization affect cell polarization and the trafficking of proteins to their sites of ultimate functional residence in renal epithelial cells in situ.
Methods: mRNA encoding MCherry-PH-AKT or MCherry-PH-PLCδ1 was injected and their distribution tracked using in vivo confocal microscopy of developing nephrons at stage 945 via fluorescence microscopy. Knockdown (KD) of PTEN, a lipid 3′ phosphate that regulates membrane PI composition, was achieved via injection of targeted morpholinos and confirmed by western blotting. The effects of PTEN KD on PH-AKT distribution were assessed in vitro. Results: In MDCK cells PH-AKT and PH-PLCδ1 localize to the basolateral and apical PMs, respectively. Their distributions are quite different in the nephrons, with both sensors showing a markedly apical signal in the proximal portion of the tubule and diffuse staining in the distal part. PH-AKT staining dramatically re-distributed to the lateral domain of renal cells upon PTEN KD but this treatment did not alter the localization of protein markers of epithelial PM polarity.

Conclusions: These studies constitute the first effort to assess the role of PI-3K in epithelial PM polarity in vivo and in vitro. These findings highlight the need to explore the processes that produce renal epithelial cell polarity in vivo and in the context of intact renal tubules.

Funding: NIDDK Support

PO0620

Autonomous Calcium Signaling in Human and Zebrafish Podocytes: Controls Kidney Filtration Barrier Morphogenesis

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Background: Mutations in nephrotic syndrome genes that lead to elevated cytoplasmic calcium in podocytes cause disruption of filtration barrier function and nephrotic syndrome. Whether calcium signaling plays a role in the initial formation of the filtration barrier is not known. Here we show that calcium signaling is active during podocyte differentiation, occurs independently of neighboring cell types, and is required for foot process and slit diaphragm formation.

Results: Immature zebrafish podocytes generated calcium transients that correlated with interactions with forming glomerular capillaries. Calcium transients persisted until 4 dpf and were absent after glomerular barrier formation was complete. Similar calcium transients were detected in maturing human organoid glomeruli suggesting a conserved mechanism. In both models, inhibitors of SEORC or IP3 receptor calcium-release channels blocked calcium transients in podocytes, while lanthanum was ineffective, indicating the source of calcium is podocyte intracellular stores. Calcium transients were not affected by deficiencies in heartbeat, endothelium or endoderm, and persisted in isolated glomeruli, suggesting that they were generated cell autonomously. Inhibition of phospholipase C gamma 1 (PLCγ1), but not Nephrin or phospholipase C epsilon1 (PLCe1), expression in zebrafish glomeruli suggests that they were generated cell autonomously. Inhibition of phospholipase C gamma 1 (PLCγ1), but not Nephrin or phospholipase C epsilon1 (PLCe1), expression in zebrafish glomeruli suggests that they were generated cell autonomously. Inhibition of PLCγ1 expression by mef2a and sinus node was not affected by injection of gentamicin into fertilized oocytes and their distributions were assessed in the developed renal tubules. With previous reports from in vitro systems. These findings highlight the need to explore the processes that produce renal epithelial cell polarity in vivo and in the context of intact renal tubules.

Funding: NIDDK Support

PO0621

Zebrafish Kidney Regeneration as a Model for Engraftment of Stem Cell-Derived Kidney Replacement Tissue

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Background: In vivo engraftment of iPS cells into mammalian kidney organoids is a novel method for stem cell-based kidney regeneration. A major challenge in engraftment is in establishing patent tubule conduits between organism graft and host tubules to allow fluid filtration and excretion. Stem cell-derived nephrons are continuously made during zebrafish kidney growth and regeneration that “plumb into” the pre-existing collecting system, making the zebrafish a viable model of kidney tissue regeneration. Using the zebrafish adult kidney to model synchronous fusion, we investigated the role of growth factor signaling pathways in this process.

Methods: Tg(Lhx1a:eGFP) expression labels directly invading ends of new nephrons. Tg(lacZ) of mCherry-β-gal transgenic zebrafish were used to trace expression of Wnt signaling domains in new nephrons. The Wnt inhibitors IWR1 and IWP2 were applied to injured adult zebrafish to test requirements for Wnt signaling. Homozygous adult Crisp/Cas9 induced mutants in faxb and mrbx were generated.

Results: We find that new nephron aggregates are patterned by canonical Wnt signaling. Cells with high canonical Wnt signaling form a single cell thick dome within cell aggregates and polarize to form rosettes with an apical constriction preceding the site of future tubule lumen. Tg(Lhx1a:eGFP) marks cells at the distal end of the new nephron which extend invasive processes or invadopodia into the underlying tubular epithelium.

Short term inhibition of Wnt signaling using IWR1 and IWP2 inhibits invadopodia formation and blocks tubulogenesis in developing nephrons. Loss of faxb and mrbx mutants exhibit ectopic distal cell proliferation and a failure of convergent extension in new nephrons after injury while Wntb mutants produce fewer new nephrogenic aggregates. A quantitative RT-PCR screen of candidate genes highly upregulated in both zebrafish proximal tubule microarrays after injury and human cancer metastasis implicates inavdopodia markers mmp14a/b, cortxin, tsk5, as well as cadh1, c-jun, and -1 in the invasion and interconnection process.

Conclusions: Wnt signaling is required for kidney tubule invasion and engraftment and in vivo expression of multiple genes associated with metastatic cell invasiveness. Manipulation of Wnt signaling is an opportunity to engineer kidney tubule interconnections.

Funding: NIDDK Support, Private Foundation Support

PO0622

Evidence for Convergence of NF-κB and Growth Hormone (GH) Signaling on Stem Cell Activation in the Adult Zebrafish Kidney

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Background: Adult progenitor cells in the mesonephric kidneys are required both during neo-nephrogenesis replacing injured tubules but also during overall growth. Single-cell RNA transcripts of adult kidney progenitor cells point to at least two receptor systems that may initiate stem cell-based nephrogenesis: growth hormone (GH) and interleukin receptors. Here we present evidence for both injury (NF-κB activation) and growth-related pathways (GH) in stimulating stem cell-based nephrogenesis.

Results: Adult zebrafish progenitor kidneys were injured by injection of gentamicin into fertilized oocytes. NF-κB signaling was determined four days post injury (dpi) by nfkb-EGFP detection of the NF-κB reporter line Tg(NF-κB:EGFP) and NF-κB-associated gene expression using qRTPCR. Requirement of NF-κB signaling during regeneration was evaluated in a chemical NF-κB antagonist. GH signaling was evaluated after either GH or gentamicin injection by quantitation of progenitor marker lhx1a:GFP in Tg(lhx1a:GFP) and stem cell marker expression by qRT-PCR. Inhibitors of GH downstream signaling were used to determine GH signaling impact after kidney injury. Bulk RNAseq from positive selected GFP+ and mcherry+ single cells by FACS was performed from kidneys 7 dpi by gentamicin injection using Tg(lhx1a:EGFP:cdh17:mCherry) fish.

Results: Gentamicin-induced kidney injury leads to an increase in tubular NF-κB nuclear translocation at 4 dpi and is associated with an upregulation of NF-κB downstream target gene expression detected by qRT-PCR. Gentamicin also causes GH receptors mRNA upregulation at 7 dpi along with the kidney progenitor markers osr1 and evx4. GH injection induced the formation of new nephrons as marked by Tg(lhx1a:GFP) expression in new nephron aggregates.

Conclusions: Multiple pathways may converge on adult kidney stem cells to activate new nephron formation. Growth and growth hormone may induce new nephron formation in response to increased body mass and need for osmoregulation. Kidney injury and nephron replacement correlate with nuclear translocation of NF-κB in injured tubules, suggesting the possibility of cytokine-mediated nephrogenesis in response to injury.

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PO0623

Dual Tubular Par1a/b cKO Is Protective Against Renal Fibrosis

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Background: Partitioning defective Par1a/b proteins are highly homologous serine threonine kinases and contribute to kidney development. Tubular Par1a/b expression increases following folic acid and unilateral ureteral obstruction (UUO). Loss of Par1a/b expression during development impairs Notch signaling pathway expression. Notch signaling activation contributes to renal fibrosis. We hypothesized that Par1a/b expression is maladaptive following injury and promotes renal fibrosis.

Methods: Using publically available single cell RNA sequencing data, we examined the cell types where Par1a (Mark3) and Par1b (Mark2) were expressed following UUO. Localization was confirmed using immunofluorescence with antibodies specific for Par1a and 1b. Conditional Par1a and 1b mice were generated using CRISPR/Cas9 gene editing. Dual tubular conditional Par1a/b knockout (cKO) mice (Pax2/rtatet/O-Cre:Mark2/lox:lox:Mark3/lox:lox) mice were generated. Deletion of Par1a (Mark3) alone or Par1b (Mark2) was confirmed following doxycycline induction. UUO was performed in adult (10 week old) male tubular Par1a/b cKO and mice; phenotype was examined at 7 days. Tubular Par1a/b deletion was induced by feeding mice doxycycline in chow starting 7 days prior to UUO. Controls were uninjured (dox) transgenic littermates and controls that were treated with dox (Mark2/lox:Mark3/lox) mice. 6-8 mice/group were studied. To detect renal fibrosis, Picro-Sirius Red staining of collagen was performed. Polarized light and Image J was utilized to quantify fibrosis on 200 images. X.

Results: Single cell analysis demonstrated increased expression of Par1a/b in proximal tubule and injured proximal tubules following UUO. This was confirmed by co-expression of Par1a inkid7 and Sox9 positive tubules following UUO. Dual tubular Par1a/b deletion was protective against fibrosis, with % fibrosis decreasing from 1.6 to 0.65 percent 7 days following UUO (p=0.0048).

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230
Conclusions: Dual Par1α/b knockout in tubules protected against fibrosis. Ongoing studies are examining optimal timing of delivery to promote repair vs. fibrosis. Par1 kinase inhibitors may be potential promising therapeutics for preventing fibrosis in chronic kidney disease.

Funding: NIDDK Support

PO0624
TRIM72-Containing Exosome for Kidney-Targeted Expression and Protection
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Background: TRIM72 is a myokine and appears to confer protection to the kidney in ischemia-reperfusion (I/R) injury. There are low levels in the kidney. We did experiments to see if TRIM72 could be transferred to the kidney so it could be used therapeutically.

Methods: Exosomes were purified from C2C12 myotubes differentiated from C2C12 myoblasts by differential centrifugation. C2C12 exosomes were given to TRIM72 null mice twice weekly for 4-weeks by tail-vein injection. Five-days post the last exosome injection, real time PCR and western blotting were used to examine tissue expression. For comparison, samples obtained from wildtype littermates served as positive controls.

Results: TRIM72 mRNA remained detectable five days post the final C2C12 exosome infusion. Moreover, TRIM72 mRNA delivered by exosomes reconstituted TRIM72 to the same organ distribution as in wildtype littermates, with high levels in kidney, skeletal muscle and moderate levels in heart and skin. TRIM72 protein expression was detected in tissues according to TRIM72 mRNA distribution. Compared to a TRIM72-deficient exosome derived from NIH3T3 condition media, treatment with C2C12 exosome mitigated high serum creatinine level of I/R injured wildtype mice. This suggested a sustained TRIM72 expression and protection in kidney when delivered in exosome format.

Conclusions: Adaptive transfer of C2C12 exosomes demonstrated TRIM72 could be reconstituted to its native organ distribution and expression in TRIM72-deficient mice. TRIM72-containing exosome mitigated elevated serum creatinine level of I/R injured mice. Pharmacologic administration of TRIM72-containing exosome might be a promising approach for the treatment of kidney disease.

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PO0625
Development of Noninvasive Clinically Applicable In Vivo Tracking of Extracellular Vesicles Using MRI
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Background: Extracellular vesicles (EVs) derived from amniotic fluid stem cells (AFSC) hold great potential for the treatment of chronic kidney diseases (CKD). We showed that AFSC-EVs are renoprotective in a mouse model of CKD, Alport syndrome. However, there is an important unmet need for real-time in vivo monitoring of these therapeutic EVs to determine biodistribution to inform about safety, targeting, and effectiveness. While current optical imaging solutions like bioluminescence and fluorescence are useful for EV tracking studies in animal models, there is limited utility in clinical applications. Here we present a novel in vivo tracking solution for therapeutic EVs in Alport mice, utilizing clinically applicable MRI technology.

Methods: To generate trackable EVs, AFSC were labeled with a novel magnetic agent (VSCM). EVs secreted by the labeled AFSC were isolated by ultracentrifugation. The viability and morphology of labeled-cells were evaluated, and the in vitro MR properties of EVs were analyzed by magnetometer. Purity, potency and identity of labeled EV was compared to non-labeled EVs. MRI biodistribution of labeled EVs was evaluated in WT and Alport mice by MRI at 10 min and 3 hr post injection, and retro-orbital and intra-cardiac routes of delivery were compared.

Results: The magnetic label did not affect the physiological characteristics of the cells and did not change identity, purity and potency (therapeutic effect in vivo) of EVs. MRI phantom studies confirmed the in vitro/ex vivo detectability of labeled EVs. Importantly, as expected MRI studies showed that EV homing to the kidney injected intra-cardiacaclly into Alport mice was more efficient vs the retro-orbital route, and Prussian blue staining of sections confirmed EV homing to the kidney.

Conclusions: We have developed a clinically applicable novel magnetic nanoparticle agent that can be used to label and track the biodistribution of EVs in the kidney and other organs using non-invasive, safe, and effective MRI technology that’s widely available. This technology is highly adaptable and can be deployed in both preclinical and clinical settings.

PO0626
Extracellular Vesicles Rescue Alport Glomerular Endothelial Lipid Dysfunction
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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD). We have previously shown that glomerular endothelial cells (GEC) are damaged in Alport syndrome mice (AS, characterized by mutations in collagen IVα3α5α5), manifested by enlarged fenestrations and damaged glyocalix in the early stage of the disease. In the present study we report on the role of altered fatty acid utilization pathways leading to GEC dysfunction in AS, and the role of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) in re-establish lipid homeostasis.

Methods: GEC were isolated from tdTomato-reporter AS and WT mice at 4 months of age by FACS and transcriptome was analyzed and compared by bulk RNA-seq. Tissue samples from patients with AS were used to confirm our findings by immunohistochemistry. In vitro, silencing experiments using human primary GEC were performed to study the role of decreased fatty acid synthase (FASN) in GEC dysfunction, and AFSC-EVs (which contain FASN in their cargo) were applied as a rescue strategy to normalize FASN level and restore lipid homeostasis. Data were confirmed using AFSC-EV biodistribution

Results: AS GEC were highly enriched for differentially expressed genes associated with cellular metabolism, and lipid metabolism in particular. Genes associated with fatty acid transport (CD36, FABP1, FABP2, FABP3) and synthesis (FASN) among others were downregulated, which was further associated with glomerular accumulation of lipid droplets in mice. We observed similar findings in human biopsy samples from AS patients by histology. In vitro, AFSC-EVs were able to rescue FASN deficiency and improve GEC function, unlike AFSC-EV lacking treatment.

Conclusions: We report for the first time a lipid metabolic dysfunction in Alport GEC, and the ability of AFSC-EVs to rescue this phenotype. Therefore, better understanding of the functional role of GEC in AS could lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

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PO0627
Administration of Mesenchymal Stromal Cell-Derived Exosomes Is an Effective Rescue Therapy for Progressive AKI in Rats
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Background: Preclinical and clinical studies have shown Mesenchymal Stem Cells (MSCs) be effective for prevention of AKI [NCT0733876]. Yet studies where MSCs are given 48 hrs. post-injury, a time at which most patients with severe AKI are diagnosed and when no rescue therapy is available, show them to be ineffective or even damaging due to compromised renal blood flow in capillary beds, where introduction of large cells has the potential to cause further deterioration of renal function [NCT01602328]. While MSCs’ renoprotection is largely due to their release of beneficial cytokines and exosomes, their potential negative impact on renal blood flow is a concern. Administration of MSC-derived exosomes is known to exert beneficial effects that are similar to those of the parent cells. We hypothesized that since MSC-derived exosomes can prevent AKI, their small size and ability to move through the microvasculature might allow them to also be an effective rescue therapy for late stage AKI where MSCs are ineffective.

Methods: MSCs from Sprague Dawley (SD) rats were used. Their purified exosomes were characterized for size by nanoparticle tracking analysis, protein concentration, gene expression of relevant markers, FACS (CD44 and CD29), and RTPCR. I/R AKI (50-52 min bilateral renal pedicle clamp) was induced in 3 groups of SD rats (6-8/group). SCr was measured at baseline, Days (D) 1 and 2. If the SCr value on D2 was greater than that on D1, then on D3, rats were given i.e. one ml of Vehicle, 4×10e10, or 2×10e9 ASCs. Studied Endpoints: SCr at Days 0-9; survival and renal injury.

Results: In contrast to what is found when MSCs are administered to rats immediately upon reflow, when administered to rats 48 hrs post-UR AKI, 2×10e9 MSCs prove ineffective at ameliorating injury, while MSC-derived exosomes significantly and sustainably improve renal function by D5 post-injury.

Conclusions: MSC-derived exosome therapy administered 2 days post-injury, when renal blood flow is compromised, but also when most clinical instances of AKI are diagnosed, is superior to MSC therapy for rescue of AKI, likely due to the mirrored paracrine content, but significantly smaller size of exosomes compared to MSCs. Our results support the hypothesis that MSC-derived exosomes could be used as a rescue therapy for non-spontaneously recovering AKI.

Funding: Commercial Support - SymbioCellTech
Human Induced Pluripotent Stem Cell-Derived Kidney Organoids to Model Idiopathic and Congenital Nephrotic Syndrome

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Background: Recent advances in human stem cell-derived kidney organoid models have opened new avenues to accurately model podocyte pathologies in 3D in vitro. The aim of this study is to develop and characterize human induced pluripotent stem cells (iPSC)-derived 3D kidney organoids as a first step in modeling idiopathic and congenital nephrotic syndrome (NS) in vitro.

Methods: Human iPSC were successfully cultured into kidney organoids and characterized using scRNA sequencing, immunocytochemistry, TEM and RNAseq. The proteome sulphate (PS) model and FSOS plasma treatment were used to model idiopathic NS. Podocin mRNA in organoids were used to study congenital NS.

Results: Kidney organoids showed a clear podocyte population expressing, amongst others, podocin, nephrin, PL2AR, WT1, VEGFA and collagen IV alpha 3. The slit diaphragm was confirmed by TEM. To model podocyte injury, organoids were exposed to podocyte necrosis specific or active SAS. Kidney organoids showed clear podocyte cytoskeletal rearrangements and the induction of pNPHIS1-1176 protein expression. The induced podocyte injury was rescued by heparin sulphate, illustrating recovery of injury associated mechanisms in 3D podocytes. The PS model was organoid-podocyte specific as their 2D iPSC-derived podocyte counterparts did not express pNPHIS1-1176. Organoids exposed to active FSOSA plasma for 4h increased granule formation, a podocyte stress marker, in NPHS1 + podocytes which was less abundant when treated with remission plasma. To model congenital nephropathy, erythroblasts from a pediatric patient with compound heterozygous mutations p.Arg138Gln (exon 3) and p.Asp160Tyr (exon 4) in the podocin (NPHS2) gene, were successfully reprogrammed in iPSC. Aberrant localization and weak podocin expression was organoid-podocyte specific as their 2D iPS-derived podocyte counterparts did not express podocin.

Conclusions: We successfully developed human iPSC-derived kidney organoids that will serve as a state-of-the-art tool to accurately study podocyte pathologies in a dish.

Funding: Other NIH Support - The Dutch Research Council

Mechanistic Elucidation of Nephron Progenitor Cell Expansion Using a Small Molecule, TCS21311, That Replaces BMP7 and Promotes Cell Proliferation

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Background: Nephron progenitor cells (NPCs) give rise to all epithelial components of the nephron, which is the smallest functional unit of the kidney. The development of a stable supply of NPCs is expected to contribute to kidney regeneration research. Although most reports on the development of NPC expansion culture use BMP7, the detailed mechanisms of action of BMP7 are unknown. To elucidate the roles of BMP7 and improve the NPC expansion culture method, we sought small molecules that can replace BMP7 in the culture system.

Methods: We isolated NPCs from Six2-GFP reporter mice and screened 4,395 chemical compounds using a previously reported expansion culture system. The activity of analogous chemicals from the hits was examined. We predicted the molecular targets of the hit compounds by chemoinformatics analyses of molecular structures. Known downstream signaling pathways were examined by immunoblotting, and differentially expressed genes (DEGs) were analyzed by removing BMP7 from the NPC expansion culture. Furthermore, we improved the expansion culture method using mouse embryonic and human induced pluripotent stem cell (iPSC)-derived NPCs by adding the hit compounds to the expansion culture condition including BMP7.

Results: The chemical screening identified a JAK3 inhibitor, CP690550, in the mouse NPC expansion culture. Although several JAK3 inhibitors as well as some JAK2/3, JAK1/2 and JAK2 inhibitors showed similar activity, one JAK3 inhibitor, TCS21311, showed especially potent effects. A structural analysis of TCS21311 confirmed that JAK3 is its primary target. A pathway analysis of the DEGs by the BMP7 removal indicated STAT3 pathway activation. The phosphorylation of Smad5/5 was increased by TCS21311 even in the absence of BMP7, suggesting a mechanism by which TCS21311 replaces BMP7 via JAK3-STAT3. Furthermore, the addition of TCS21311 to the expansion culture containing BMP7 resulted in more efficient proliferation of mouse embryonic and human iPSC-derived NPCs.

Conclusions: These results will contribute to understanding the roles of BMP7 in NPC proliferation and to the stable supply of NPCs.


Stromal-mediated processes are critical in determining fibrosis progression. Stromal cells are essential for kidney development and homeostasis, but are also myofibroblast precursors and their maladaptive responses tip the balance from tissue repair to scarring. Our work shows that GATA3 is crucial for developing and mature renal stromal cells and its primary target. A pathway analysis of the DEGs by the BMP7 removal indicated STAT3 pathway activation. The phosphorylation of Smad5/5 was increased by TCS21311 even in the absence of BMP7, suggesting a mechanism by which TCS21311 replaces BMP7 via JAK3-STAT3. Furthermore, the addition of TCS21311 to the expansion culture containing BMP7 resulted in more efficient proliferation of mouse embryonic and human iPSC-derived NPCs.

Conclusions: These results will contribute to understanding the roles of BMP7 in NPC proliferation and to the stable supply of NPCs.


PO0631

The Transcription Factor GATA3 Regulates Hyaluronan-Mediated Stromal-Cell Responses During Kidney Injury, Repair, and Fibrosis

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Background: Stromal-mediated processes are critical in determining fibrosis progression. Stromal cells are essential for kidney development and homeostasis, but are also myofibroblast precursors and their maladaptive responses tip the balance from tissue repair to scarring. Our work shows that GATA3 is crucial for developing and mature renal stroma and its expression marks a distinct fibroblast subset associated with improved tissue outcomes following injury. Hyaluronan-(HA), a matrix glycosaminoglycan, is a key regulator fibroblast heterogeneity and predominance of distinct HA synthase (HAS) isoform expression separates fibroblasts into subsets which mediate fibrosis progression or resolution. Here, we investigated GATA3+ fibroblasts in relation to factors that regulate HA-matrix synthesis and metabolism during fibrosis progression versus prevention.

Methods: Immunohistochemistry was performed on rat kidneys with bilateral ischemia-reperfusion-injury +/- ischemic preconditioning (IPC) or BMP7 administration (prevention models). Primary human fibroblasts were used to test the role of GATA3 in BMP7 antagonism of TGFβ-driven myofibroblast differentiation. RNA and plasmids were used for knockdown or over-expression. HA levels were correlated with fibrosis profiles using ELISA, RT-qPCR and immunofluorescence.

Results: GATA3+ fibroblasts increased in abundance during regenerative phase following injury, co-stained for PDGFRβ and surrounding repaired tubules. More GATA3+ PDGFRβ fibroblasts were observed in prevention models suggesting a protective, anti-fibrotic role. In prevention models, prominent co-localisation was observed between GATA3 and HAS1 in VSMCs, distal tubules and a distinct stromal population. In contrast, GATA3 expression was attenuated in α-SMA+ myofibroblasts in chronic fibrotic lesions where HAS2 was prominent. In vitro, BMP7 induced GATA3 expression and GATA3 knockdown attenuated BMP7-driven antagonism of TGFβ-driven myofibroblast differentiation, in part by increasing HAS2 expression and pericellular HA. HAS2 promoter analysis confirmed enrichment of GATA binding motifs.

Conclusions: GATA3+ fibroblasts represent a distinct stromal subset and mediating the reno-protective effects of IPC and BMP7 on IRI-induced renal damage by modulation of HA-matrix and HAS isomer expression.
PO0632

The Regenerative Response to Renal Injury of the African Spiny Mouse Is Epigenetically Regulated Through H3K27 Methylation

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Background: Lysine methylation of histones plays an important role in regulating gene expression. When tri-methylated, chromatin regions marked by H3K27me3 are inaccessible for transcription. EZH2 of the Polycomb group methylates H3K27, with opposing action carried out by histone demethylases JMJD3 & UTX. EZH2 activation and subsequent increase in H3K27me3 has been associated with renal fibrosis. We hypothesize that in the African spiny mouse, a mammalian model of kidney regeneration, demethylation of H3K27 is associated with regenerative wound healing after ischemia-reperfusion kidney injury.

Methods: Experiments were carried out on kidneys of spiny mouse and house mouse in normal kidneys and kidneys 1 & 3 days after unilateral ischemia-reperfusion injury. Mass spectrometry was used to profile histone modifications. Expression of key genes involved in methylation of H3K27 were quantified using RNA-sequencing, and protein concentration was quantified by western blot. H3K27me3 marks were visualized by immunofluorescent staining. Genes marked by H3K27me3 were identified using CUT&RUN ChIP-sequencing.

Results: H3K27me3 is significantly increased in mouse kidney after ischemia reperfusion injury whereas no change in the repressive mark was noted in spiny mouse when quantified by mass spectrometry and western blot. H3K27me3 marks are abundant in fibrotic mouse kidneys and distributed throughout kidney tissue, while H3K27me3 is reduced in repaired kidneys of spiny mouse. RNA-sequencing demonstrated a 4-fold increase in Eh2 in mouse after injury vs 2-fold increase in spiny mouse. During the course of injury, JmjD3 expression increased in spiny mouse but decreased in expression in mouse. We previously identified nephrogenic progenitor genes potentially associated with regenerative wound healing in spiny mouse, including Cdhl, Cdhl6 and H19. CUT&RUN identified these genes as repressively marked by H3K27me3 in mouse but available for transcription in spiny mouse.

Conclusions: This work suggests that the regenerative response to renal injury in spiny mouse is orchestrated at least in part through the methylation of histone H3K27. Modification of the histone methylation landscape through small molecular modulators may redirect the outcome of kidney injury from fibrosis to regeneration.

Funding: NIDDK Support

PO0634

Effect of Hypoxia Preconditioning on Angiogenesis and Senescence in Human Adipose Tissue-Derived Mesenchymal Stem Cells

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Background: Hypertension(HTN) and chronic kidney disease(CKD) alter the angiogenic and immunomodulatory properties of human adipose-derived Mesenchymal Stem Cells(AMSC). Hypoxic conditions modify growth potential, paracrine functions and gene expression of AMSCs. We tested the hypothesis that AMSCs in CKD patients, preconditioned with hypoxia, will have reduced senescence, enhanced migratory, proliferative and angiogenic functions compared to healthy kidney donors.

Methods: We cultured AMSCs(P3-4) from healthy kidney donors(Control), patients with HTN and CKD(n=6 each group) under normoxia(20%O2) and hypoxia(1%O2) to compare 5-hmC differences between MSC groups.

Results: The table shows characteristics of enrolled patients. Hypoxia suppresses AMSC migration in support and HTN patients while enhancing it in CKD patients and increasing proliferation in all groups. Hypoxia increases VEGF secretion in controls and CKD while downregulating HGF gene expression in controls and HTN group. In CKD patients, TGF-β secretion was higher at baseline and under hypoxia, TNF-α was elevated. Senescence(gene expression of P16,P12) was not different among the groups at baseline but hypoxia attenuated it in all groups.

Conclusions: Hypoxic preconditioning of AMSCs increases migration, proliferation, upregulates VEGF secretion and gene expression, and downregulates pro-senesence genes. These results support hypoxic preconditioning to enhance the regenerative potential and overcome challenges in autologous stem cell therapy for nephropathies.

Funding: NIDDK Support
PO0635

In Vivo Data to Support Induced Pluripotent Stem Cell-Derived Renal Progenitors as Potential Cell Therapy for Kidney Disease


Background: Novel therapies are needed to deliver life changing medicines to renal patients and cell therapy is a relatively new strategy of kidney therapy. We have developed novel methodology to produce kidney organoids for target validation. Here we have used this learning, to derive human renal progenitor cells (RPCs) and examine their differentiation in vivo using 2 delivery models.

Methods: We used iPSC modified to contain a GFP reporter of nephrin expression, to generate human RPC differentiated to day 6 and 10 using a previously described kidney organoid protocol. We then used kidney capsule implantation and intravenous delivery in naive and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶) and time (1 and 5 weeks). For IRI, we infused i.v RPC (5x10⁶) directly after kidney clamping (24mins), reperfusion and measured systemic biodistribution of RPC at 2 and 25 days. Other readouts included kidney RNAseq, renal function, plasma cytokines and histology.

Results: We can currently show RPC implanted in kidney capsule continue differentiation to day 10. Using histology and RNAseq signatures, there is some enrichment towards tubular like cells particular at high dose, using day 10 matured progenitors at 5 weeks after implantation. These include differentiation of tubular transporters, such as nucleoside (ENT1) and water-transporting proteins (AQP1). In IRI experiments, i.v infusion was well tolerated with normal disease course based on increases in plasma creatinine, BUN and urinary KIM-1. Biodistribution and differentiation analysis is underway, focused on anti-human nuclear staining in multiple organs and qPCR. Plasma inflammatory, cardiac and renal biomarkers analysis will examine any IRI infiltrate response.

Conclusions: These observations clearly demonstrate the use and differentiation potential of RPC in a pre-clinical setting. These studies may aid design and delivery modality, for any future effort in examining RPC therapy for renal disease

Funding: Commercial Support - Manchester BIOGEL, Government Support - Non-U.S.

PO0637

Gelatin Methacryloyl (GeMA) as a Tunable Biophysical Environment for the Derivation of Human Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: The translational utility of hiPSC-derived kidney organoids relies on our ability to comprehensively mimic both the biochemical and biophysical properties of the cellular milieu in vitro. An improved understanding of how the mechanical environment affects the renal progenitor niche during development and how perturbations to such biophysical environments effects cell fate are required. Within this context, Gelatin methacrylate (GeMA), a derivative of collagen, represents a mechanically amendable scaffold to probe cell fate dynamics.

Methods: We proposed that kidney organoids were differentiated within photo-crosslinked GeMA hydrogels of defined mechanical strengths. Hydrogels were characterised using rheological analysis and SEM. Enrichment of renal cell types in response to the various mechanical microenvironments was subsequently investigated, with real-time monitoring of cell fate dynamics. Proliferation and differentiation were assessed using qRT-PCR and immunofluorescent analysis. Significant enrichment of MEIS1/2/3+ve interstitial cells was noted in organoids differentiated within stiffer hydrogels. Interstitial expansion and increased extracellular matrix deposition was confirmed using H&E and Masson’s trichrome staining within stiff GeMA scaffolds.

Conclusions: We propose the utility of GeMA hydrogels as faithful extracellular supports for the specification of hiPSC-derived kidney organoids. These scaffolds represent a mechanically tuneable microenvironment to investigate the effects of the biophysical milieu on renal development and disease perturbations.

Funding: Government Support - Non-U.S.

PO0636

Synthetic Peptide Hydrogels as Support Matrices for the Generation of Distinct Cell Populations Within Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: Kidney organoids that display improved maturity with reduced variability are needed to produce models that faithfully mirror the in vivo organ. We propose that organoid development will benefit from the introduction of a bioinformally controlled cell niche. Synthetic self-assembling peptide hydrogels (SAPHs) are ideal systems to support organoid development that more accurately mimics the in vivo environment due to the simplicity of the structure formed at the molecular level, their ease of fabrication and tunability. These materials are fully defined and tunable, fully defined microenvironment. Synthetic self-assembling peptide hydrogels are ideal systems to support organoid development that more accurately mimics the in vivo environment due to the simplicity of the structure formed at the molecular level, their ease of fabrication and tunability. These materials are fully defined and tunable, fully defined microenvironment. Synthetic self-assembling peptide hydrogels are ideal systems to support organoid development that more accurately mimics the in vivo environment due to the simplicity of the structure formed at the molecular level, their ease of fabrication and tunability.

Methods: Peptide hydrogel properties were investigated via transmission electron microscopy and rheology. Organoids were characterized by immunofluorescence and low immunogenicity, cell-retention, biodegradability, and tuneable mechanical properties.

Results: The formulated hydrogels. Hydrogels comparable to the stiffness of the gastrulation-stage embryo (Gₐ = 400 Pa), human tissue (Gₐ = 2.5 kPa) and fibrotic tissue (Gₐ = 8-10 KPa) were generated. SEM revealed that hydrogel pore size was dependent on starting gelatin concentration in the hydrogel formulations. PCR and qPCR and cleaved caspase-3 staining of organoids embedded within scaffolds confirmed high cell proliferation and viability in all hydrogel constructs by day 26 of differentiation. The formation of glomerular, proximal tubular and distal tubular structures, that were supported by basement membrane and interstitial cells was confirmed in all conditions using qRT-PCR and immunofluorescent analysis. Significant enrichment of MEIS1/2/3+ve interstitial cells was noted in organoids differentiated within stiffer hydrogels. Interstitial expansion and increased extracellular matrix deposition was confirmed using H&E and Masson’s trichrome staining within stiff GeMA scaffolds.

Conclusions: We propose the utility of GeMA hydrogels as faithful extracellular supports for the specification of hiPSC-derived kidney organoids. These scaffolds represent a mechanically tuneable microenvironment to investigate the effects of the biophysical milieu on renal development and disease perturbations.

Funding: Government Support - Non-U.S.

PO0638

Generation of Chimeric Nephrons in Newborn Mice for Testing Drug-Induced Nephropathy

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Background: Studies have reported certain limitations of experiments on animals for assessing nephropathy. Due to species differences in tubular transporters, a model for chronic nephropathy in humans is desirable. Organoids are a promising novel research method, but the absence of their connection to the urinary tract makes them difficult for use in the evaluation of chronic nephropathy. Therefore, our goal was to develop a new pre-clinical assessment model that is amenable to repeated dose toxicity studies. In particular, this model aimed to produce human nephrons chimerized in the kidneys of host animals. We previously reported “ex vivo utero” cell transplantation in which exogenous renal progenitor cells (RPCs) were transplanted into the retroperitoneal cavity of mouse fetuses without lethality. Although transplanted cells differentiated into functional nephrons chimerized with host-resident cells, this method requires proficiency. In this paper, because continuous nephrogenesis takes place over several days after birth in mice, we used newborn mice as host animals and conducted a proof-of-concept study using mouse RPCs.

Methods: Mouse metanephroi extracted from green fluorescent protein (GFP)-labeled mouse embryos were dissociated into single RPCs and injected into the subcapsular areas of newborn mice at postnatal days 0–1. After 2 weeks, kidneys of host mice containing

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
exogenous nephrons were extracted for the immunohistochemical evaluation. In addition, cisplatin was administered intraperitoneally to the host mice and the response of exogenous proximal tubular cells (PTCs) was evaluated.

**Results:** Immunohistochemistry revealed around 10% chimerism in glomeruli, proximal and distal tubules in the injected areas. Exogenous PTCs exhibited dose-dependent repression of Kim-1 in response to cisplatin administration. We aim to subsequently report data from single-cell RNA sequencing.

**Conclusions:** Mouse exogenous RPCs could form chimeric nephrons in newborn mice that reproduced drug-induced nephrotoxicity seen in native kidneys. The neo-tubules are expected to be a tool that can be applied to long-term repetitive drug administration because of its integration into the host functioning nephrons.

**Funding:** Government Support - Non-U.S.

**PO0641**

Maturen-Enhanced Proximal Tubules Enable Functionality, Toxicity Screening, and Infectious Disease Modeling in Kidney Organoids

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**Background:** The highly specialised proximal tubule (PT) nephron segment is responsible for most kidney functions in mammals and is acutely vulnerable to disease, making it a key objective for toxicity screening and disease research. While induced pluripotent stem cell (iPSC)-derived kidney organoids (KO) have been established, the PT remains immature with limited evidence of functional transporters. Here we report the development of PT-enhanced organoids with nephron functionality, enabling improved modelling of PT-relevant conditions including drug-induced toxicity and infection such as SARS-CoV-2.

**Methods:** Standard and fluorescent reporter iPS lines were subjected to prolonged monolayer differentiations (modified from: Howden et al. EMBO Rep 2019; Vanslambrouck et al. JASN 2019) and precisely-timed morphogens for targets such as β1 VAMP and NOTCH pathways prior to organoid generation (Takasato et al., Nat Protoc 2016). Maturation was analysed via immunofluorescence, live confocal imaging of fluorescent reporters, transcriptional profiling, transporter function assays, and SARS-CoV-2 infectivity.

**Results:** Prolonged nephron progenitor differentiation with simultaneous prevention of spontaneous nephrogenesis resulted in PT-enhanced kidney organoids with elongated and aligned nephrons. Striking proximo-distal nephron orientation resulted from localised WNT antagonism. Improved upregulation of PT-specific markers compared to standard organoids was strengthened by evidence of transport function (specific uptake of albumin, organic cations, and cilia-facilitating appropriate K1 MUP) regulation. This approach also improved expression of SARS-CoV-2 entry factors, confirmed by susceptibility to infection and viral replication.

**Conclusions:** We describe enhanced kidney organoids with improved PT maturity arising from alterations to early mesodermal patterning and delayed nephron initiation. The enhanced conditions also provided more stringent control over nephron spatial arrangement. PT-enhanced organoids provide an ideal model to better understand human PT maturation, inherited and acquired PT disease, and drug toxicity implications.

**PO0642**

Estrogen-Related Receptor Gamma Identified as a Novel Link Between Ciliogenesis and Nephron Development

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**Background:** Ablation of cilia, hair-like projections that facilitate mechano- and chemo-sensing, has been linked to developmental disorders, kidney dysfunction, and renal cyst formation. Since prostaglandin signaling has been noted as a key regulator of ciliogenesis, we investigated potential upstream factors that could contribute to both kidney and cilia development. One nuclear receptor, Errγ, was of particular interest, as it interacts with known ciliogenic factors and causes renal cysts in mouse knockout models.

**Methods:** We confirmed that Errγ does indeed affect endogenous prostaglandin levels through an ELISA assay of Errγ deficiency models. We also assessed the effect of Errγ deficiency using whole mount in situ hybridization to characterize changes in specific nephron cell populations. We used immunohistochemistry to quantify aberrant cilia formation, cell polarity, and cell turnover in the kidney, ear, and nose. We utilized qRT-PCR to measure changes in transcription of potential downstream targets, and used overexpression or chemical treatments to rescue these targets or their products to further support regulatory effects.

**Results:** Errγ deficiency embryos had decreased endogenous PGE2 levels and exhibited nephron composition defects including expanded expression of proximal markers and reduced distal segments. These were likely due to changes in cell fate choice, as no changes in cell death or proliferation were found. The formation of renal cilia was also disrupted, where both cilia length and number of ciliated basal bodies were significantly reduced in ciliated cell populations. Interestingly, Errγ was required for ciliogenesis in other tissues as well, as cilia length was also decreased in the node and the ear. These phenotypes were consistent with a disruption of prostaglandin signaling.
Methods: Passaged cells that were to be used to treat diabetic NOD/SCID mice were characterized for gene expression profiles by rPET. For in vivo testing, NOD/SCID mice were made diabetic with STZ, then randomized based on blood glucose levels into groups of 6 each, treated with insulin pellets, and once blood glucose levels were stabilized near normal animals were treated i.p. either with $2\times10^{5}$ human cell-derived NIs/kg bw (n=6) or vehicle (n=6), then followed for 8 weeks. Once blood glucose levels were decreed to be no longer significantly improved compared to controls without administration of exogenous insulin, mice in each group were again treated with either $2\times10^{5}$ NIs/kg bw or vehicle, and followed for an additional 6 weeks. Therapeutic efficacy was assessed by survival, 2x weekly blood glucose monitoring, and glucose tolerance tests administered 57 and 41 days post the 1st and 2nd doses, respectively.

Results: Human NI therapy significantly improved glycemic control and survival vs. vehicle. A 2nd dose given to the initial group normalized blood glucose levels long-term.

Conclusions: Despite the limitations of the diabetic NOD/SCID model, these data show that human NIs are curative, and in conjunction with data from the dog study, where allogeneic NI therapy reduces the need for insulin without need for antirejection drugs, have high translational relevance and support the planned conduct of human NI clinical trials.

Funding: Commercial Support - SymbioCellTech

PO0645

IL-33 as a Novel Target for the Treatment of Diabetic Kidney Disease

Barbara Musial,1 Asha Selvaraj,2 David J. Baker,2 Stephanie C. Heasman,4 James Conway,1 Tim Sidel,1 Xiaozen Wang,1 Dustin K. Seth,1 David B. Westenfelder,2,3,4 Anna Gooch,2 University of Utah Hospital, Salt Lake City, UT; 236 J Am Soc Nephrol 32: 2021

Background: Diabetic kidney disease (DKD) has classically been thought as a microvascular disorder, although inflammation has emerged as a key pathophysiological mechanism involved in the development of diabetic kidney injury. Consequently, inflammatory mediators have aroused as promising therapeutic targets.

Methods: IL-33 is a broad acting cytokine, expressed in endothelial and epithelial barriers, that mediates local tissue inflammation. It exerts its function by binding to a heterodimer formed by its specific receptor ST2 and co-receptor IL-1RAcP. Due to the evidence of the role of IL-33 in kidney injury, we generated MEDI3506, a potent IL-33 blocking mAb for the treatment of DKD.

Results: Transcriptomic analysis showed that expression of IL-33 RNA is upregulated in both the glomeruli and tubulointerstitium of DKD patients in two independent cohorts. Assessment of expression in both human and experimental DKD demonstrated that IL-33 is among the most regulated inflammatory genes. Preliminary data on IL-33 protein levels in human kidney biopsies indicates that IL-33 is increased in DKD versus controls. Preclinically, the db/db uninephrectomy model of DKD showed IL-33 protein levels in kidney lysates positively correlated with histological glomerular damage from week 7 to 21. More importantly, blockade of ST2 signalling by using a mAb, prevented the progression of albuminuria. In vitro mechanistic studies using primary human glomerular endothelial cells (GECs) and mesangial cells (MCs) showed that both cell types expressed ST2 and upregulated IL-33 in response to TNF-α and IFN-γ, commonly upregulated in diabetic kidney microenvironment. Moreover, GECs and to a lesser extent MCs, displayed a significant IL-33 induced proinflammatory cytokine release (e.g. IL-8, IL-6...) mediated by MAP kinase activation and NF-κB translocation. All these effects were inhibited by MEDI3506.

Conclusions: Upregulation of IL-33 in diabetic kidney, generates localised chronic kidney inflammation through autocrine signalling in GECs and MCs. This data suggest that targeting IL-33 with MEDI3506 arises as a promising therapeutic intervention for DKD, currently in Ph2b trial.

Funding: Commercial Support - AstraZeneca

Graphical Abstract

PO0644

Treatment of Diabetic NOD/SCID Mice with Human “Neo-Islets,” 3D Organoids of Mesenchymal Stromal and Pancreatic Islet Cells, Normalizes Blood Glucose Levels: Significance for Clinical Trials

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Background: We reported that allogeneic “Neo-Islets” (NI) are immune protected and permanently correct autoimmune diabetes in NOD mice by omental engraftment and endocrine cell redifferentiation. This new “endocrine pancreas” delivers islet hormones physiologically into the hepatic portal vein. Further, treatment of insulin-dependent dogs with allogeneic canine NIs (ongoing FDA-approved Pilot Study) consistently improved glycemic control without the need for antirejection drugs. The current preclinical study aimed to test whether human NIs can also restore euglycemia, and (b) whether redosing of suboptimally controlled diabetic animals could restore euglycemia in streptozotocin (STZ)-diabetic NOD/SCID mice, as has been previously shown for mouse and dog cell-derived NIs.

PO0643

Single-Cell Analysis of Senescent Epithelia Reveals Targetable Mechanisms Promoting Fibrosis

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Background: Progressive fibrosis and maladaptive organ repair result in significant morbidity and millions of premature deaths annually. Senescent cells accumulate with age and after injury and are implicated in organ fibrosis, but the mechanisms by which senescence influences repair are poorly understood. Here, we address the role of senescence in maladaptive repair and identify new anti-fibrotic targets.

Methods: We analyse human kidney tissue samples post deobstruction and corresponding murine models to test involvement of senescent cells in maladaptive repair via pharmacological depletion. We use single cell RNA-Seq to examine these cells in more detail. We validate our findings using in-vitro models of senescence and fibroblast activation. Finally we use murine models of injury to test inhibition of in silico targets as anti-fibrotic.

Results: We demonstrate for the first time in man that senescence and fibrosis persist in kidneys in the aftermath of a resolved obstructive injury. Using a relevant murine model of injury and repair we show senescent epithelia persist after relief of ureteric obstruction and that depletion of senescent epithelia reduces fibrosis and promotes repair. We next characterise senescent epithelia in murine renal repair using single cell RNA-Seq for the first time. We extend our classification to human kidney and liver disease, identifying conserved pro-fibrotic molecules which we validate in vitro and in human disease. Inhibition of one of these molecules is essential for TGF mediated fibroblast activation. Consequently we demonstrate that temporarily inhibition, in vivo significantly reduces kidney fibrosis after injury. Our data shed light on the role of senescent epithelia in renal disease and identify a new anti-fibrotic molecule.

Conclusions: Analysis of signaling pathways of senescent epithelia connects the important pathways such as the cell stress response to organ fibrosis, permitting rational design of anti-fibrotic therapies.

Funding: Private Foundation Support

PO0644

Human Disease Senolytic Mouse model Single Cell RNA-Seq Novel Anti-fibrotic Therapy

Graphical Abstract
PO0646
Endogenous Interleukin 33 Contributes to the Progression of Diabetic Nephropathy
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Background: Interleukin-33 (IL-33) is a pleiotropic cytokine involved in the pathogenesis of diabetic nephropathy. IL-33 has been shown to induce inflammation and promote glomerulosclerosis. However, the exact role of IL-33 in the development of diabetic nephropathy remains unclear.

Methods: In this study, we investigated the role of IL-33 in the progression of diabetic nephropathy using a mouse model. We performed renal biopsy at the early stage of diabetes to determine the expression of IL-33 and its downstream targets.

Results: Our results showed a significant increase in the expression of IL-33 in diabetic mice compared to control mice. Furthermore, mice treated with an IL-33 inhibitor had a reduced progression of diabetic nephropathy.

Conclusions: These findings suggest that IL-33 plays a critical role in the progression of diabetic nephropathy and may be a potential therapeutic target.

PO0647
Beneficial Effects of Tumor Necrosis Factor α Blockade in a Mouse Model of Diabetic Nephropathy
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Background: Diabetic nephropathy is a common complication of diabetes mellitus that leads to end-stage renal disease. TNF-α has been implicated in the pathogenesis of diabetic nephropathy, but the role of TNF-α blockade in vivo has not been fully elucidated.

Methods: Akita-ReninTg mice were used as a model of diabetic nephropathy. Mice were treated with etanercept, a TNF-α inhibitor, and the effects on renal function and histology were assessed.

Results: Etanercept treatment significantly reduced albuminuria and improved renal function in diabetic mice. Additionally, histological analysis showed reduced glomerulosclerosis and interstitial fibrosis in the etanercept-treated group.

Conclusions: These findings suggest that TNF-α blockade may have beneficial effects in the treatment of diabetic nephropathy.

PO0648
A Novel Anti-Inflammatory Renoprotective Effect of GLP-1 Receptor Agonists in Type 1 Diabetes: Shifting Macrophage Polarization
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Background: Macrophage polarization has been implicated in the progression of diabetic nephropathy. GLP-1 receptor agonists (GLP-1RAs) have shown promising renoprotective effects in experimental models of diabetes.

Methods: We evaluated the effects of GLP-1RAs on macrophage polarization in a mouse model of type 1 diabetes. Renal macrophage polarization was assessed using flow cytometry and immunohistochemistry.

Results: GLP-1RAs treatment shifted macrophage polarization towards an anti-inflammatory phenotype, characterized by increased M2 polarization markers.

Conclusions: These findings suggest that GLP-1RAs may have renoprotective effects by modulating macrophage polarization in diabetic nephropathy.

PO0649
Interferon-γ Signaling and the Progression of Early Diabetic Kidney Disease
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Background: Interferon-γ (IFN-γ) signaling has been implicated in the progression of diabetic kidney disease. However, the role of IFN-γ signaling in early diabetic kidney disease remains unclear.

Methods: We used a mouse model of type 2 diabetes to assess the effects of IFN-γ on kidney function and histology. Renal expression of IFN-γ pathway markers was assessed using quantitative PCR.

Results: IFN-γ signaling was upregulated in the early stages of diabetic kidney disease. Blockade of IFN-γ signaling improved renal function and reduced histological signs of kidney injury.

Conclusions: These findings suggest that targeting IFN-γ signaling may be a promising strategy for the prevention of diabetic kidney disease.

PO0762
Increased Circulating IL-33 Levels in Type 2 Diabetes Mellitus
Zixuan Zhu, Peking Union Medical College Hospital, Dongcheng-qu, China.

Background: IL-33 is a cytokine involved in the regulation of innate immunity. Increased circulating IL-33 levels have been observed in type 2 diabetes mellitus.

Methods: Serum levels of IL-33 were measured in patients with type 2 diabetes mellitus and compared to healthy controls.

Results: Patients with type 2 diabetes mellitus had significantly increased circulating IL-33 levels compared to healthy controls.

Conclusions: These findings suggest that IL-33 may play a role in the pathogenesis of type 2 diabetes mellitus.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO0650**

**Nrf2 Activators Induce Inflammasome Attenuation: Possible Role in Diabetic Nephropathy**


**Background:** Kidney diseases remain a worldwide public health problem characterized by sustained inflammation. Inflammation has recently emerged as crucial regulators of renal inflammation. In particular, the NLRP3 inflammasome, is involved in the activation of caspase-1 and the maturation of IL-1β and IL-18, which have been strongly associated with diabetic nephropathy. DJ-1 is a redox-sensitive chaperone with reported antioxidant and anti-inflammatory properties in the kidney, in part due to the regulation of transcription factor Nrf2, which regulates the expression of several antioxidant genes. The 20 amino acid (aa) peptide ND-13, is a new experimental treatment against the regulation of transcription factor Nrf2, which regulates the expression of several antioxidant genes. The 20 amino acid (aa) peptide ND-13, is a new experimental treatment against the regulation of transcription factor Nrf2, which regulates the expression of several antioxidant genes.

**Methods:** ND-13 is the medium used by the stimulation of the NLRP3 inflammasome by LPS/ATP, and decrease in macrophages pre-treated with Bardoxolone (1µM), Diabetic Kidney Disease: Basic - I J Am Soc Nephrol 32: 2021.

**Results:** The IL-1β concentration is the medium increased by the stimulation of the NLRP3 inflammasome by LPS/ATP, and decreased in macrophages pre-treated with Bardoxolone (65.0±26.4ng/ml, n=6, P<0.05) but not in macrophages pre-treated with ND-13. Concentration-response curve demonstrates the capacity of Bardoxolone to inhibit NLRP3 inflammasome activation by LPS/ATP. Additionally, in presence of H2O2 (100nM), ND-13 significantly decreased IL-1β release after NLRP3 activation (88.6±4.2%, n=4, P<0.05), suggesting the capacity of the ND-13 peptide to reduce NLRP3 inflammasome activity under pathological conditions. PBMcs isolated from the blood of controls patients, patients with diabetes, and patients with diabetes and renal disease were cultured in vitro and stimulated with LPS/ATP. Compared to controls and diabetic individuals, patients with diabetic nephropathy presented a trend to increase IL-1β release.

**Conclusions:** All these data point out that inflammasome pre-activation could have a role in the pathogenesis of diabetic nephropathy, that Nrf2 pathway stimulation is a promising approach to decrease immune cells inflammasome pre-activation, and ND-13 could be a new approach to protect the renal damage associated to inflammasome over-activation in renal diseases.

**Funding:** Government Support - Non-U.S.

**PO0651**

**Activation of STING Causes Proteinuria in Mice and Contributes to Diabetic Kidney Disease**

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**Background:** Diabetic kidney diseases (DKD) is one of the major health problems worldwide with no current cure. Podocytes express elements of the innate immune system which may contribute to chronic inflammation and glomerular damage. Stimulator of interferon genes (STING) was identified as a crucial regulator of the DNA sensing pathway which may contribute to chronic inflammation and glomerular damage. Stimulator of activation in renal diseases.

**Methods:** STING-specific antagonist, and ND-13 (1µM) for 24 hours.

**Results:** In vitro and stimulated with LPS/ATP. Compared to controls and diabetic individuals, patients with diabetic nephropathy presented a trend to increase IL-1β release. Mice were IP-injected with C-176 (750nM), STING-specific antagonist, for 4 weeks daily. Single dose of c-diAMP (25mg/kg) and sacrificed 72h after injection. 16-week-old db/db mice were IP-injected with a single dose of c-diAMP (25mg/kg) and sacrificed 72h after injection. 16-week-old db/db mice were used to evaluate the role of AcSDKP, an additional group of db-nko were treated for 8 weeks with S17092, an inhibitor of prolyl-oligopeptidase that forms AcSDKP. After HS, MAP, renal eNOS expression, IL-6, and the macrophage M1/M2 ratio of db-nko/S17092 were similar to db mice. Finally, to evaluate whether the absence of the ACE N-domain affects immune or non-immune renal cells, db mice were transplanted with a bone marrow (BM) of db-nko while db-nko received a db BM. Strikingly, db-nko with db BM developed salt sensitivity but db with db-nko BM remained salt resistant (MAP after HS: 121±8 vs. 107±4 mmHg, P<0.05). The absence of salt sensitivity in db with db-nko BM was associated with less IL-6 levels and lower M1/M2 macrophage ratio in the kidney.

**Conclusions:** Thus, blocking the ACE N-domain and the consequent AcSDKP accumulation in immune cells, may lead to activation of the cGAS-STING pathway. Treatment of C57BL6 mice with c-diAMP treatment to inhibit STING (10 µM), an Nrf2 inducer, and ND-13 (1 µM), strongly associated with diabetic nephropathy. DJ-1 is a redox-sensitive chaperone that protects against oxidative stress by modulating the expression of antioxidant genes. The 20 amino acid (aa) peptide ND-13, is a new experimental treatment.

**Funding:** Other NIH Support - NHLBI

**PO0653**

**Renal Type 1 Pericytes in the Development of Diabetic Kidney Disease**

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**Background:** Pericytes are described as regulators and keepers of the vascular system. They can recognize and respond to inflammatory stimuli, through secretory and phenotype alterations. So far, the involvement of pericytes during diabetic kidney disease (DKD) has not been demonstrated yet, as well as how they can change its inflammatory and phenotypic profile in this condition. In addition, not much is known about how these cells trigger DKD-associated injury and inflammation.

**Methods:** DKD was induced in NG2-Dored mice by the combination of unilateral nephrectomy (UNx) and multiple low doses of streptozotocin (50 mg/kg). UNx controls were treated with vehicle. All the mice were followed for 12 weeks. Urine glucose, protein/creatinine and albuminuria were evaluated as markers of renal function. NPHS1, KIM-1, IL-6, PKM2, HK2, CPT1a and LDH (qPCR), pericyte frequency/phenotype/secretion profiles (FACS) were assessed in kidney samples.

**Results:** DKD mice had an increased in protein/creatinine ratio, as well as in glucosuria when compared to non-DKD mice (p<0.01). The impaired renal function was accompanied by reduction in NPHS1 gene expression (p<0.05). Moreover, we observed increase in PKM2, HK2 and IL-6 expression (p<0.05). FACS analysis revealed increase in relative and absolute numbers of CD146+/NG2+ cells (p<0.05), as well as an increase of type 1 pericytes (NG2+ Nestin−), when compared to non-DKD mice (p<0.05).

**Conclusions:** Type 1 pericytes seem to contribute to DKD progression, through IL-6 secretion and TGF-β conversion from LAP-1. However, it is still necessary to evaluate the metabolic profile of pericyte during the DKD progression and how this cells communicate with other renal cells. 

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.

238
PO0654

Follistatin, an Activin A Antagonist in an Accelerated Mouse Model of Diabetic Kidney Disease
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Background: We previously demonstrated that circulating activin A, an inflammatory mediator implicated in cellular senescence-induced adipose tissue dysfunction and profibrotic kidney injury, is increased in human diabetic kidney disease (DKD) and directly correlates with kidney dysfunction. We hypothesized that follistatin, an activin A antagonist, could negate the injurious effects of activin A in DKD.

Methods: An accelerated type 2 diabetes (db/db, 10-week-old) mouse model was generated by implantation of osmotic minipumps loaded with angiotensin (Ang)-II (1000 ng/kg/min, n=14). Mice were randomized to intraperitoneal follistatin (5ug/g) or vehicle at days 15 and 18 post-pump with euthanasia at day 28. Kidney injury markers included: proteinuria, kidney injury marker (KIM)-1, tumor necrosis factor soluble receptor 1 (TNFsR1), collagen I and histological changes were measured. Kidney gene expression of activin A and macrophage chemotactrant protein-1 (MCP-1) were measured by qPCR.

Results: Implantation of AngII (db/dbAngII) pumps induced proteinuria, mesangial matrix expansion, glomerular sclerosis, and increased fibrosis in db/db mice compared to saline-pump controls (db/Saline; Figure 1A-D). Collagen I, TNFsR1, MCP-1, KIM-1, and activin A gene expression was increased in db/db mice (Figure 1E). Follistatin therapy reduced activin A gene expression and other kidney markers in addition to morphology. Conclusions: Follistatin attenuated diabetic kidney injury, reduced activin A expression and decreased macrophage chemotactransitants. Activin A may be a novel therapeutic target for halting DKD progression.

Funding: NIDDK Support, Other NIH Support - DiaComp

PO0655

The Functional Role of Neat1 in Diabetic Kidney Disease
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Background: Long non-coding RNA Nuclear Paraspeckle Assembly Transcript 1 (Neat1) is a central mediator of DKD, but its inhibition is not feasible due to adverse effects. Thus, indirect methods of attenuation are of current interest.

Results: Neat1 plays a pathogenetic role in DKD and its knock-down could attenuate diabetic-induced tubular fibrosis and may be a potential therapeutic strategy for diabetic nephropathy.

Funding: Government Support - Non-U.S.

PO0656

Cell Surface GRP78 Regulates TGF-β1-Mediated Profibrotic Responses via TSP-1 in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses plays a central role in its pathogenesis. We recently showed that the endoplasmic reticulum resident GRP78 translocates to the cell surface in response to HG, where it mediates Akt activation and downstream profibrotic responses in MC. Transforming growth factor β1 (TGFβ1) is recognized as a central mediator of HG-induced profibrotic responses, but whether it is regulated by cell surface GRP78 (csGRP78) is unknown. TGFβ1 is stored in the ECM in a latent form, requiring release for biological activity. The matrix glycoprotein thrombospondin-1 (TSP-1) is an important factor in TGFβ1 activation, known to be increased in DKD and by HG in MC. Here we determined whether csGRP78 regulates the expression of TSP-1 and thereby TGFβ1 activation in HG.

Methods: Primary rat and mouse MC were treated with 30mM HG. TSP-1 upregulation and deposition into the ECM and TGFβ1 activation were assessed using standard molecular biology techniques.

Conclusions: TSP-1 transcript and promoter activity were increased by HG, as were cellular and ECM TSP-1, and these required P38/K Akt activity. To determine whether csGRP78 was required, its activity was inhibited using vaspin or the C-terminal targeting antibody C38. Alternatively, GRP78 translocation to the cell surface was prevented with siRNA knockdown of its transport chaperone MTJ1. All of these prevented HG-induced TSP-1 upregulation and deposition into the ECM. The HG-induced increase in active TGFβ1 in the medium was also inhibited, and this was associated with reduced intracellular Smad3 activation and signaling.

Conclusions: These data support an important role for csGRP78 in regulating HG-induced TSP-1 transcriptional induction via P38/K Akt signaling. Functionally, this enables TGFβ1 activation in response to HG, with consequent increase in ECM proteins. Means of inhibiting csGRP78 signaling represent a novel target for preventing the DKD-associated fibrosis. TGFβ1 is a central mediator of DKD, but its inhibition is not feasible due to adverse effects. Thus, indirect methods of attenuation are of current interest.

Funding: Government Support - Non-U.S.
PO0658

Recombinant Slit2 Attenuates Renal Fibrosis in a Mouse Model of Diabetic Nephropathy

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Background: We recently described Akita+/- Ren-/- mice as a model that replicates many features of human diabetic nephropathy (DN), including hyperglycemia, hypertension, albuminuria, reduced glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Previously, we showed that recombinant N terminal Slit2 (Slit2) inhibited renal fibrosis in mouse models of postischemic renal fibrosis and obstructive uropathy. To date, however, the anti-fibrotic effects of Slit2 have not been tested in a model of DN. Here we examine the effects of Slit2 therapy in the Akita+/- Ren-/- mouse.

Methods: At 6 weeks of age, Akita+/- Ren-/- mice and Akita-/-Ren-/- mice were randomized to receive three weekly intraperitoneal injections of Slit2 (2 ug) or saline, and followed for a further 20 weeks.

Results: When compared with saline-treated Akita+/− Ren−/− mice, Slit2-treated Akita+/− Ren−/− mice demonstrated improved survival (66.67% vs 50%) and decreased systolic blood pressure (142±6.1mmHg vs 167±8.5 mmHg). Structurally, Slit2-treated Akita+/− Ren−/− mice displayed decreased glomerulosclerosis (glomerular microsclerotic red score: 0.22±0.02 vs 0.28±0.02) and interstitial fibrosis (picrosirius red staining: 0.08±0.01 vs 0.10±0.01, a-smooth muscle actin (aSMA) staining: 0.02±0.00 vs 0.05±0.01, and vimentin staining: 0.11±0.01 vs 0.15±0.01). Slit2 treatment attenuated the nuclear translocation of the pro-fibrotic factor YAP (26.44±7.87% vs 66.20±7.63%) and TAZ (28.55±2.99%, vs 71.42±7.90%, a marker of YAP/TAZ activation) in aSMA-positive fibroblasts in mouse kidneys. In vitro, Slit2 decreased TGF-β-induced YAP and expression of aSMA, a marker of YAP/TAZ activation (7.39% vs 80.2±3.4%).

Conclusions: Taken together, our results show that Slit2 attenuates diabetic kidney fibrosis, possibly through inhibition of fibroblast YAP and TAZ activity.

PO0660

Role of GRP56 in Glomerular Endothelial Cell Injury in Diabetic Kidney Disease

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Background: GEC injury is a key pathogenic event in early diabetic kidney disease (DKD). However, the mechanisms of GEC injury in DKD remain unclear and the treatments by targeting specifically GEC injury are lacking.

Methods: By taking advantage of transgenic mice expressing enhanced yellow fluorescent protein (EYFP) under the endothelial-specific Flk1 promoter, we were able to sort GECs from both control and diabetic mice for RNA sequencing. We identified G-protein coupled receptor-56 (GRP56) as a highly upregulated gene in diabetic GECs. Then, we confirmed the role of GRP56 in GEC injury in DKD by both in vitro and in vivo studies.

Results: We searched the recent single-cell RNA-seq data and confirmed that GRP56 expresses predominantly in GECs in the glomeruli. We found that both mRNA and protein expression of GRP56 increased in human DKD and correlated negatively with eGFR, suggesting an important role of GRP56 in human DKD. In cultured GECs, GRP56 expression was upregulated by high glucose and advanced glycation endproducts (AGE). Collagen III, a major ligand of GRP56, was able to suppress eNOS phosphorylation and expression through activation of GRP56. We demonstrated that GRP56 reduced eNOS phosphorylation likely through G12/13-mediated RhoA pathway and inhibited eNOS expression via G- mediated inhibition of aMAPK/PAK/MLK4 pathway in cultured GECs. In vivo, knockout of GRP56 attenuated albuminuria and glomerular injury and restored expression of eNOS and KL4 in GECs in mice with DKD.

Conclusions: Taken together, these findings suggest a critical role of GRP56 and its underlined mechanism in regulation of GEC injury in early DKD.

Funding: NIDDK Support, Veterans Affairs Support

PO0661

Transcriptional Profiling of Renal Endothelial Compartments During Progression of Murine Diabetic Nephropathy

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Background: Kidney endothelial cell (EC) injury and capillary rarefaction are key pathogenic events in diabetic nephropathy (DN). The molecular mechanisms and spatial and temporal patterns of EC responses in DN remain elusive. We hypothesized that single-cell RNA sequencing (scRNAseq) would reveal transcriptional changes in specific kidney EC populations during murine DN progression.

Methods: Kidney EC (n=5,464) collected from 6-, 11-, and 20-week-old BTHR ob/ob mice and lean littermates were analyzed by scRNASeq using SmartSeq2. By a combination of established markers, immunofluorescence, and in situ hybridization, we ascribed anatomical identity to EC clusters assigned by Pagoda, assessed their individual transcriptional changes during disease progression, and performed Ingenuity Pathway Analysis.

Results: We identified EC clusters corresponding to afferent and efferent arterioles, glomerular and peritubular capillaries (PTC), ascending and descending vasa recta, veins and lymphatics. BTBR ob/ob mice developed progressive PTC rarefaction. Analysis of differentially expressed genes (DEGs) and pathway activity allocated most DN-associated changes to PTC and glomerular EC. Intriguingly, several consistent DEGs showed differential up- and downregulation depending on cell type and disease stage (Fig. 1). E.g., whereas glomerular EC showed DN stage-dependent activation of IFG1 signaling and inflammation, IFG1 signaling and cell cycle progression were inhibited in PTC-EC.

Conclusions: Using high-resolution scRNASeq, our study provides insight into the complexity and diversity of responses in different EC compartments during progression of DN, which may help pinpoint new therapeutic targets.

Funding: Commercial Support - AstraZeneca Gothenburg, Sweden

PO0659

Impact of Mineralocorticoid Receptor Antagonism in a New Model of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the most prevalent form of chronic kidney disease and is associated with cardiovascular diseases. Several studies reported beneficial effects of mineralocorticoid receptor (MR) antagonists in DKD, indicating the importance of aldosterone/MR axis in this pathology. To study the metabolic and renal alterations in a new model of DKD and explore the effect of the MR antagonist canrenoate.

Methods: Sham or 5/6 nephrectomy was performed in 6 weeks old C57Bl6J mice. HbAc1 was higher in the Nx-HFD group vs Sham or Nx, an effect prevented by canrenoate (see table). The glucose tolerance was impaired in NX-HFD vs Sham or 5/6 nephrectomy was performed in 6 weeks old C57Bl6J mice.

Results: HbAc1 was higher in the Nx-HFD group vs Sham or Nx, an effect prevented by canrenoate (see table). The glucose tolerance was impaired in NX-HFD vs Sham or 5/6 nephrectomy was performed in 6 weeks old C57Bl6J mice.

Conclusions: Using high-resolution scRNASeq, our study provides insight into the complexity and diversity of responses in different EC compartments during progression of DN, which may help pinpoint new therapeutic targets.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.
PO0662
Transcriptomic Alterations of Angiogenesis Activity in Human Mesenchymal Stromal/Stem Cells in Diabetic Kidney Disease
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Background: Therapeutic interventions that optimize angiogenic activities may reduce rates of end-stage kidney failure and extremity amputations in individuals with diabetic kidney disease (DKD). Autologous mesenchymal stromal cells (MSCs) infusion is a promising novel treatment, but DKD-related factors, including hyperglycemia and uremia, might alter MSC angiogenic repair capacity.

Methods: To explore MSC angiogenic dysregulation in DKD, we characterized the transcriptome of adipose tissue-derived MSC obtained from DKD subjects (DKD-MSC) compared to age-matched controls without diabetes or kidney impairment. Next-generation RNA sequencing (RNA-seq) was performed to identify in MSCs differentially expressed (DE; adjusted p<0.05, |log fold change| >1) mRNA and miRNA involved in angiogenesis (GeneCards). DE miRNAs were further inspected to identify targets expressed (DE; adjusted p<0.05, |log fold change| >1) mRNA and miRNA involved in angiogenesis (GeneCards). DE miRNAs were further inspected to identify targets involved with angiogenesis genes (miRWalk and Ingenuity pathway analysis).

Results: Mean age in DKD subjects was 65±8 years, 31% were females, and mean eGFR was 38±15.4 mL/min/1.73m² (n=29), while control subjects (n=9) had higher eGFR (80±13.3 mL/min/1.73m²; p<0.0001). RNA-seq analyses revealed 133 DE mRNAs (77 up- and 56 down-regulated) in DKD-MSC compared to Control-MSC. Figure 1A shows the top 30 DE mRNAs. Of 208 DE miRNAs, 14 (Figure 1B) regulated miR-30c-5p and miR-5p.

Conclusions: MSC from individuals with DKD may have limited angiogenic potential and reparative capacity, warranting caution in autologous MSC transplantation in DKD.

Funding: NIDDK Support, Private Foundation Support

PO0663
Contribution of Endothelial ADAM17 in a Pre-Diabetic Mouse Model
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Background: ADAM17 activates inflammatory and fibrotic processes through the shedding of various molecules such as TNF-α or TGF-β. In physiological situations, ADAM17 is expressed mainly in the distal tubular cell while, in renal damage, its expression increases throughout the kidney including the endothelium. Galectin 3 (Gal3) is a lectin that is postulated as a biomarker of kidney damage. Its overexpression in diabetic nephropathy could be a compensatory mechanism for damage induced by reactive oxygen species (ROS). To characterize, for the first time, an experimental mice model fed with high-fat diet (HFD) with deletion of ADAM17 in endothelial cells and to describe the expression of kidney Gal3.

Methods: After 25 weeks of HFD, glycemia, glucose tolerance, body weight, albuminuria, glomerular microscopy (PAS staining) and Gal3 (immunohistochemistry) were analyzed in 15 wild-type (WT) mice and 15 endothelial ADAM17-KO mice.

Results: HFD mice had higher glucose levels, glucose intolerance, and higher body weight compared to standard diet (SD) mice. Moreover, HFD increased albumin/creatinine ratio in WT mice compared to ADAM17-KO mice. At the glomerular level, WT mice with HFD had bigger glomerular size and mesangial matrix expansion. In contrast, the deletion of ADAM17 prevented the increase in glomerular size and decreased the mesangial area and index. Gal3 increased its expression in ADAM17-KO mice on both SD and HFD mice (see table).

Conclusions: The deletion of ADAM17 in endothelium prevents the appearance of glomerular hypertrophy, expansion of the mesangial matrix, albuminuria and increases the expression of Gal3 in the renal cortex. The increase in the expression of Gal3 could be a compensatory mechanism for the lack of activation of the EGFR/TNFR pathway in the endothelium ADAM17-KO model.

PO0664
Apolipoprotein C3-Rich Low-Density Lipoprotein Is Elevated in Diabetic Kidney Disease Patients and Enhances Endothelial Cell Injury
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Background: Diabetic dyslipidemia plays a pathogenetic role in the development and perpetuation of diabetic kidney disease (DKD). Apolipoprotein CIII (ApoC3), a component of triglyceride-rich very-low-density and low-density lipoprotein, expression by glucose may contribute to diabetic dyslipidemia. Early endothelial damage is also associated with progression of DKD. Thus, we want to study the effect of ApoC3-rich low-density lipoprotein (AC3RL) on DKD and its underlying molecular mechanisms.

Methods: Plasma samples were obtained from clinically stable patients with DKD recruited at our outpatient clinic. AC3RL was isolated from plasma low-density lipoprotein with the affinity-purified method.

Results: Level of plasma AC3RL were significantly higher in DKD patients than in control subjects (Figure; p<0.05). AC3RL induced endothelial cells (ECs) apoptosis and reduction of the fenestrated endothelium. The level of phosphorylation of IKKa, p53 and Cleaved Caspase-3 (CC3) were markedly increased in AC3RL-induced ECs (p < 0.05 vs. control; n = 4). The contribution of P-IKKα, p53, and CC3 in AC3RL-mediated apoptosis were blocked in ECs transfected with si-IKkα.

Conclusions: AC3RL elevation may be a risk factor for DKD, and inhibiting IKKa may be novel protect endothelial damage and arrest DKD progression.

Funding: Clinical Revenue Support
Identification of Cell-Specific Transcriptomic Changes and Cross-Talk in Diabetic Mice with Podocyte-Specific Induction of KLF6 Using Single Nuclear RNA Sequencing

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Background: Krippel-Like Factor 6 (KLF6), a zinc finger transcription factor, is a key regulator of cytochrome c oxidase assembly in the podocytes. We previously reported that podocyte-specific loss of KLF6 exacerbates diabetic kidney disease (DKD). However, the role of podocyte-specific induction of human KLF6 in DKD remains unexplored.

Methods: A combination of unilateral nephrectomy and streptozotocin (UNx-STZ) was utilized to induce DKD in mice. Using the “Tet-on” system, mice with podocyte-specific induction of human KLF6 (hKLF6PODTA) were generated by crossing NPHS2-rtTA mice with tre- hKLF6 mice and fed with doxycycline-containing diet. UNx-STZ-NPHS2-rtTA and SHAM Unx-veh mice served as diabetic and non-diabetic controls, respectively. Single nucleated (snRNA) libraries were prepared from kidney cortex using the 10x Chromium System. Raw sequencing data was aligned to mouse pre-mRNA reference genome using Cell Ranger. Quality control, dimensionality reduction and clustering were performed using the R-package, Seurat.

Results: 23 clusters were generated using unsupervised clustering analysis. Enrichment and pathway analyses showed a downregulation of injury-related pathways as well as inflammatory and interleukin signaling in the UNx-STZ-treated hKLF6PODTA group across the podocyte, endothelial cell, mesangial cell, and proximal tubular clusters, compared to the UNx-STZ-treated NPHS2-rtTA group. Conversely, metabolic pathways such as oxidative phosphorylation and fatty acid metabolism were upregulated. A cross-reference of the differentially expressed genes (DEGs) in the podocyte cluster of the UNx-STZ-treated hKLF6PODTA group with a KLF6 ChIP-seq data set revealed the presence of putative KLF6 binding sites in the regulatory regions of several DEGs. A unique proximal tubule (PT) cluster with distinctive gene expression signature was identified in the hKLF6PODTA group, suggesting an intercellular communication between podocytes and the PT cells in the hKLF6PODTA group that mediates the progression of DKD.

Conclusions: SnRNA-seq demonstrates potential mechanisms by which podocyte-specific induction of KLF6 attenuates the progression of DKD.

Funding: NIDDK Support

An Accelerated Method of Podocyte Differentiation from Human Induced Pluripotent Stem Cells for Modeling Diabetic Nephropathy

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Background: Podocytes are highly specialized visceral epithelial cells that maintain glomerular barrier function and play important roles during both kidney development and progression of glomerular disease. Mature podocytes extracted from mammalian kidneys are difficult to culture long-term, hindering research on podocytepathies. Establishing an alternative, inexhaustible source of podocytes would be a valuable tool for understanding the molecular mechanisms underlying specific podocytepathies and developing targeted therapies. The discovery of induced pluripotent stem cells (hiPSCs) led to several protocols for deriving podocytes from hiPSCs, which could potentially serve as an unlimited source of podocytes.

Methods: All the existing effective methods for hiPSC-derived podocytes either require prolonged culture times (~30 days) or expensive media. Therefore, we sought to develop a faster and less expensive method. We found a simple and effective method to derive podocytes from hiPSCs in twelve days of culture and at lower cost. Our method followed a stepwise protocol in which the hiPSCs were differentiated into primitive streak followed by intermediate mesoderm using activation of Activin A and Wnt signaling. Intermediate mesoderm cells were treated with FGF9 to generate neuron progenitors, followed by a cocktail of established growth factors to finally derive mature podocytes.

Results: The developed podocytes expressed podocyte markers including PODX, synaptopodin, MABF, Nephin at protein levels comparable to the existing methods. Flow cytometry analysis revealed that our method results in generation of ~80% mature glomerular podocytes. We confirmed the functionality of the hiPSC-derived podocytes via permeability assay for FITC-albumin uptake. Next, we treated the cells with media containing high glucose (~150mM) to generate a hiPSC-derived podocyte model of diabetic nephropathy. The podocytes showed actin rearrangement upon treatment with high glucose, suggesting the ability of these cells to effectively model podocytepathies. In addition, treatment with high glucose resulted in increased cytoketosis and reduced viability in the podocytes.

Conclusions: Altogether, we have discovered a faster and less expensive method of podocyte differentiation from hiPSCs, as well as a new tissue culture model of diabetic nephropathy for disease modeling.

Funding: Private Foundation Support

The Contribution of Proximal Tubular ADAM17 in a Pre-Diabetic Mouse Model

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Background: Both acute and chronic kidney lesions induce an increase in ADAM17 that cleaves several transmembrane proteins, among them molecules related to inflammatory and fibrotic pathways. Our group demonstrated that in experimental type 1 diabetes, inhibition of ADAM17 decreases inflammation and renal fibrosis. Indeed, this protease is proposed as a possible therapeutic tool for the treatment of kidney disease. However, its role in pre-diabetic stages has not been fully analyzed.

Methods: In a knockout mouse model for tubular ADAM17 fed with high-fat diet (HFD), we determined glycemia, glucose tolerance, body weight, hypertrophy and mesangial expansion (PAS staining) and the number of podocytes (immunohistochemistry), after 25 weeks of a follow-up (n = 15 WT, n = 15 KO).

Results: Wild-type (WT) mice on HFD had higher body weight and higher glycemia with dysregulation of glucose homeostasis compared to mice on standard diet (SD). At the glomerular level, WT mice with HFD had greater glomerular size and mesangial expansion. In contrast, the deletion of ADAM17 in the proximal tubular cell improved glucose
tollereance and protected against glomerular injury. The loss of podocytes observed in WT mice with HFD was not observed in HFD-mice with deletion of ADAM17 (see table).

Conclusions: The conditional knockout of ADAM17 at the proximal tubule level improves glucose tolerance and reduces kidney lesions typically observed in diabetes such as glomerular hypertrophy, mesangial expansion and podocytes loss, in a murine model with high-fructose diet-induced pre-diabetes. ADAM17 may therefore have an inducing role in pre-diabetic kidney injury.

PO0669
The Role of Cytoskeleton-Associated Protein 4 in the Glomerulus and Diabetic Kidney Disease
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Background: Cytoskeleton-associated protein 4 (CKAP4) was first discovered in the kidney, and is critical for actin filament formation downstream of glomerular basement membrane repair upstream and downstream of GSDMD.

Methods: Western blot analysis for CKAP4 expression was performed on proximal tubule samples from diabetic and healthy rats. CKAP4 expression was also assessed in human glomeruli using immunohistochemistry.

Results: CKAP4 expression was upregulated in diabetic rat kidneys compared to healthy controls. In human glomeruli, CKAP4 expression was elevated in patients with diabetic nephropathy compared to healthy controls.

Conclusions: CKAP4 plays an important role in the pathogenesis of diabetic kidney disease by regulating actin filament formation and basement membrane repair.

PO0670
Store-Operated Ca2+ Entry Contributes to High Glucose-Induced Podocyte Injury
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Background: Diabetic Nephropathy is one of the major microvascular complications of diabetes and the most common cause of end stage renal disease. Hyperglycemia is a known pathogenic stimulus for onset and progression of diabetic nephropathy. Podocyte injury is one of early features of the disease. However, the mechanism of the diabetes-induced podocyte injury is not fully understood. Store operated Ca2+ entry (SOCE) has multiple functions in both excitable and non-excitable cells. This ubiquitous Ca2+ signaling includes two key components, ORAI1 (a plasma membrane protein mediating SOCE) and STIM1 (an ER membrane protein sensing Ca2+ level in the ER lumen). Previous studies have demonstrated that alterations in SOCE are involved in cell dysfunction in many cell types. However, whether and how SOCE contributes to podocyte injury in diabetes is not known. The objective of this study was to determine that excitable and non-excitable components of SOCE mediated high glucose (HG)-induced podocyte injury by upregulating calpain activity.

Methods: All experiments were performed using cultured human podocytes. Western blot was conducted to estimate ORAI1, STIM1 and nephrin protein abundance. Ca2+ imaging was used to analyze Store- and SOCE-mediated cytosolic calcium signals. Confocal microscopy was used to visualize podocyte actin arrangement. Calpain activity was determined by calpain activity assay kits. Results: HG (25mM) treatment significantly increased ORAI1, but not STIM1 protein abundance for time periods ranging from 2 to 12 hours. The HG-induced ORAI1 response was dose dependent. Ca2+ imaging experiment showed that HG treatment for 2 hours increased SOCE. In addition, HG treatment significantly decreased nephrin (a podocyte marker) protein abundance and resulted in cytoskeleton rearrangement by formation of cortical F-actin. Both HG responses were significantly blunted by BTP2 (4 µM), an SOCE inhibitor. Furthermore, we found that activation of SOCE by thapsigargin (1 µM) decreased calpain activity which was abolished by BTP2. In addition, BTP2 blunted the increased calpain activity induced by HG treatment. Moreover, calpeptin (a calpain inhibitor) attenuated the HG-induced reduction of nephrin protein abundance.

Conclusions: The present study suggests that enhanced SOCE contributes to HG-induced podocyte injury by increasing calpain activity.

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PO0671
HDAC6 Inhibition with CAY10603 Alleviates Renal Fibrosis Against Pyroptosis in Tubular Injury
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Background: The essential role of tubular damage has been highlighted during the progression of chronic kidney diseases (CKD), included diabetic nephropathy (DN), but the treatment options are still limited.

Methods: We interrogated the connectivity Map (CMap) with tubular transcriptomic profiles of biopsy-proven DN to identify a drug to reverse the regulated genes in tubulointerstitial component of DN. The effects of potential drug were validated in vivo STZ-induced early and late stage diabetic CD-1 male mice, as well as in non-diabetic mice with adenine-induced LPS-induced septic kidney injury.

Results: CAY10603, a specific inhibitor of histone deacetylase 6 (HDAC6), was identified as a drug to reverse the signature in both early- and late-stage DN. In patients with DN and mice with KD, renal tubular expression of HDAC6 was significantly upregulated. In vivo, 5mg/kg dosage of CAY10603 significantly ameliorated tubular injury and tubulointerstitial fibrosis, reduced tubulointerstitial α-SMA and collagen I expression, and infiltration of F4/80 macrophages in both early and late stage of diabetic kidney disease. In addition, CAY10603 also conferred renoprotection in non-diabetic mice including adenine-induced CKD and LPS-induced septic kidney injury. Mechanically, in vitro HK-2 cells, HDAC6 inhibition with CAY10603 regulated NLRP3 activation and membrane repair upstream and downstream of GSDMD.

Conclusions: Collectively, CAY10603 exhibited therapeutic potential against pyroptosis in tubular injury

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PO0672
FRMD3/Protein 4.1O Increases Hippo Signaling in a Glucose-Dependent Manner
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Background: FRMD3 is a candidate gene for diabetic nephropathy and encodes for protein 4.1O. Different splice variants 204, 207, 201 are expressed in the kidney cortex. Previous data show that protein 4.1O links nephrin to the actin cytoskeleton. In diabetic kidney disease Hippo signaling is increased. Phosphorylated Yes-associated kinase (YAP) and its nuclear targets TAZ are suppressed in diabetics.

Methods: Glomeruli and proximal tubules from patients with diabetic nephropathy and healthy controls were analyzed via immunohistochemistry for protein 4.1O expression. Changes in protein expression were analyzed via mass spectrometry and western blot, and the morphology of the actin cytoskeleton via immunofluorescence.

Results: The expression of human CKD cohort revealed that protein 4.1O was down regulated in glomeruli from patients with diabetic kidney disease (DKD), but not in the other diseases investigated. CKAP4 was expressed by all glomerular cells, but to lesser extent in endothelial cells. KD of the zebrafish CKAP4 homolog rendered the fish proteinuric and led to podocyte effacement. KD of CKAP4 in human podocytes and mesangial cells led to loss of actin stress fibers in both cell types. In addition, the expression of several growth factor receptors was affected, with a prominent loss of PDGF receptors in the mesangial cells reducing their proliferative response to PDGF.

Conclusions: Our results from the in vivo and in vitro experiments show that reduced expression of CKAP4 leads to glomerular dysfunction and changes in the actin cytoskeleton. In podocytes, this is known to cause foot process effacement which we observed. Less is known about how dysregulation of the actin cytoskeleton affects the mesangial cells, but we found that mesangial cells with KD downregulated other cytoskeletal PDGF receptors, and had a reduced proliferative capacity. A subset of patients with KD have a low expression of CKAP4, we suggest that CKAP4 regulation can be a part of the disease development and progression.

Funding: Private Foundation Support, Government Support - Non-U.S.
Human Proximal Tubular Cells in a 3D In Vitro Culture as a Model for Exploring Diabetic Lesions

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Background: We have previously demonstrated the beneficial effect of ADAM17 deletion on human proximal tubular kidney cells (HKC-8) in 3D in vitro spheroids incubated with high glucose resembling the human kidney diabetic environment. Galectin-3 (Gal-3) is a pro-fibrotic protein and modulates the activity of fibroblasts and macrophages in chronically inflamed organs through activation of the TGF-β/Smad3 pathway and it is postulated as regulator of cardiac oxidative stress which can facilitate the development of fibrosis. Also, Dynamin related protein 1 (DRP-1) is a key regulator of the mitochondrial fission and ATP production under stress condition. As ADAM17 has been associated with TGF-β modulation during renal fibrosis, we wanted to evaluate the effect of ADAM17 deletion on Gal-3, Fibronectin and DRP-1 in HKC-8 spheroids incubated under high glucose conditions

Methods: ADAM17 deletion of renal tubular cells was performed using the CRISPR/Cas9 technology. HKC-8 cells grew inside an RGD-functionalized dextran hydrogel to obtain 3D spheroids. 13 days post-seeding, the spheroids were incubated with 35mM of D-glucose (HG), 5mM of D-glucose (LG) or 35mM of mannitol as osmotic control for 72h. Immunofluorescence for Gal-3, pDRP-1 and Fibronectin was performed

Results: HG increased the expression of fibronectin and pDRP-1 and tends to increase Gal-3 in wild-type (WT) spheroids. Interestingly, ADAM17 deletion decreased fibronectin expression in spheroids incubated with HG as compared to WT spheroids. Moreover, ADAM17 deletion abrogates the effect of HG on Gal-3 expression (see table and images, scale bar 50µm). The osmotic control, mannitol, did not affect the expression of the analysed proteins

Conclusions: ADAM17 blockade protects against fibrosis by decreasing fibronectin and Gal-3 and modulated the mitochondrial dynamic in human kidney tubular spheroids under high glucose conditions

PO0674

Animal Models Cannot Well Reflect the Transcriptomic Changes of Human Diabetic Nephropathy: A Comparative Study

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Background: Various mouse models have been developed and widely applied in investigating the pathogenesis of DN. Whether the models share the same underlying molecular changes with human DN is poorly understood. To this end, we performed a systematic analysis of the transcriptomes of the kidney tissues from patients with DN and various mouse models. To our knowledge, this is the largest analysis on this topic

Methods: This study included the bioinformatic analysis and in vivo validation. We comprehensively analyzed the genome-wide mRNA expression of kidney tissues collected from patients with biopsy-proven DN and widely used animal models(n=60). The bioinformatics workflow is shown in figure 1. Then, the expression levels of interested genes were further validated

Results: The transcriptomic profiles of all the animal models had poor correlation with those of patients with DN. However, we observed a much better correlation within species, regardless of the disease stages or modeling methods. In the GSVA analysis, we found the animal models shared similar pathological processes but could not well reflect the real circumstances in human DN. In enrichment analysis, we found the animal models shared the same pathways such as the accumulation of extracellular matrix and MAPK signaling with human DN. However, these models can not well mimic pathways such as cytokine signaling, vitamin D metabolism and SLC transporter disorders. Finally, the expression levels of the interested genes measured by the westernblot method showed good consistency with those generated by high throughput platforms

Conclusions: We found mouse models can not well reflect the transcriptomic changes of human DN in many aspects. We also provided a useful dataset to facilitate the translational research of DN

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0675

Integrative Transcriptome Analysis Reveals Involvement of Spermatogenesis-Related Genes in Diabetic Nephropathy

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Background: Cell heterogeneity has impeded the accurate interpretation of the bulk transcriptome data from patients with diabetic nephropathy (DN). We performed an analysis by integrating bulk and single-cell transcriptome datasets to uncover novel mechanisms leading to DN, especially in the podocytes.

Methods: Microdissected glomeruli and tubules transcriptome datasets were selected from Gene Expression Omnibus (GEO). Then the consistency between datasets was evaluated. The analysis of bulk dataset and single-nucleus RNA dataset was integrated to reveal the cell type-specific responses to DN. The candidate genes were validated in kidney tissues from DN patients and diabetic mice.

Results: We compared 4 glomerular and 4 tubular datasets and found considerable discrepancies among datasets regarding the differentially expressed genes (DEGs), involved signaling pathways and the hallmark enrichment profiles. Deconvolution of the bulk data revealed that the variations in cell-type proportion contributed greatly to this discrepancy. Integrative analysis uncovered that the dysregulation of spermatogenesis-related genes, including TEKT2 and PIAS2 was involved in development of DN. Importantly, the mRNA level of TEKT2 was negatively correlated with the mRNA levels of nephrin (r = -0.66, p<0.0001) and podocin (r = -0.85, p<0.0001) in human diabetic glomeruli. Immunostaining confirmed that the expression of TEKT2 and PIAS2 were up-regulated in podocytes of DN patients and diabetic mice.

Conclusions: The integrative strategy can help us to efficiently use the publicly available transcriptomics resources. Using this approach, we identified TEKT2 and PIAS2, two spermatogenesis-related genes involved in the pathogenesis of DN.

PO0676

Understanding Genetic Mechanisms of Diabetic Nephropathy at the Single-Cell Level

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Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease worldwide. Susceptibility to DN is inherited but genetic determinants have not been clearly defined. We have previously described a mouse model combining Akita-REN transgene (AR) that exhibits human DN features including albuminuria, glomerulosclerosis, and genetic predisposition. Susceptible (S) 129 strain AR mice develop overt DN whereas resistant (R) C57BL/6 AR mice are largely free of kidney damage.

Methods: We performed single-cell sequencing of glomerular cell obtained from the wildtype (WT) and AR mice from both S and R strains at 10 weeks of age before overt pathological abnormalities are present in S mice.

Results: A total of 60,682 cells were sequenced from the four conditions. Within the main glomerular cell lineages: podocytes, mesangial and endothelial cells, there were distinct functional clusters corresponding to the S and R strains (see figure). Within the S but not R strain, well-defined cell clusters derived from AR and WT were identifiable within podocytes and mesangial cells, while in other cell types, the impact of strain was much greater than diabetes and renin-angiotensin activation in driving differential gene expression. Gene networks defining the strain differences have potential functional relevance in the development of glomerular diseases. For example, in podocytes, gene networks related to cytokineskeleton are activated in the R strain, whereas the S strain shows upregulated oxidative stress responses. A number of candidate genes identified in human DN and other inherited nephropathies are also differentially expressed on the S and R backgrounds.

Conclusions: Single-cell sequencing analysis of glomerular cells from a DN mouse model has identified cell-specific transcriptomic profiles linked to genetic susceptibility and resistance to DN, suggesting causal mechanisms. Substantial overlap with pathways and candidate genes linked to human DN suggest that this model can be useful for understanding genetic pathophysiology of DN in humans.

Funding: Government Support - Non-U.S.

PO0677

Altered Cellular Signaling Pathways Identified by Proteomics and Phosphor-Proteomics in a Rat Model of Diabetic Kidney Disease

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Background: Alterations of cellular signaling are associated with onset and deterioration of various types of disorders, which could be the targets for new drug development and discovery. Currently, post-translational protein modification and glycosylation are identified by comprehensive proteomic analyses. Since diabetic kidney disease (DKD) is the leading cause of chronic end stage renal disease, exploring novel signaling pathways involved in the initiation and progression of DKD may have therapeutic potential. In the present study, we probed renal tissue in a DKD rat model for altered signaling cascades using proteomics and phosphor-proteomics analyses.

Methods: The animal model of type 2 diabetes melitus, Spontaneously Diabetic Torii Fatty (SDT Fatty) rats were uninephrectomized at 9 weeks of age, and then from 10 weeks of age, 0.3% NaCl was added to drinking water to exacerbate DKD progression for additional 5 weeks (Group A) or 10 weeks (Group B). After the treatment period, blood was collected for biological measurements and kidney tissue was obtained for histology and proteomics and phosphor-proteomics analyses.

Results: In SDT Fatty rats, the stage of DKD was classified as ‘early’ (Group A) or ‘advanced’ (Group B) by SUN levels and expansion of mesangial matrix and glomerular cell size. The expression of the 'serpin family' as serine protease inhibitors and the 's100 family' as RAGE ligands were newly detected by functional annotation clustering determination (P<0.05). In addition, five cascades including pathways of 'microRNA in cancer' indicated by Crk, Hnrnpk and Marcks at early stage and two cascades including 'RNA transport' indicated by Ccsl3, Efd3 and Eif5a at advanced stage were detected by phosphor-proteomics analysis in KEGG database (P<0.05).

Conclusions: These findings demonstrate that several groups of known and new signaling cascades may have important roles for the initiation and/or progression of DKD.

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PO0678

NETosis Contributes to the Pathogenesis of Diabetic Kidney Disease: A Proposed Mechanistic Pathway

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Background: Diabetic kidney disease (DKD) is one of the most debilitating complications of diabetes. Considerable research has focused on the key role of NADPH oxidases (NOXs) in DKD. Of note, our group has demonstrated the role of mTOR signaling pathway in mediating NOX-derived reactive oxygen species (ROS) production in DKD. Inflammation and an overactive immune response are known to be major risk factors for the development and progression of DKD. Recently, NETosis, a novel neutrophil-specific cell death process, was described to be associated with inflammation and diabetes. However, the effect of NETosis on DKD remains uninvestigated. Interestingly, increasing evidence highlights a pivotal role for the mTORC1 pathway and NOXs in regulating NETosis. Herein, we hypothesize that hyperglycemia activates the mTORC1/NADPH oxidase signaling pathway, leading to excess neutrophil extracellular traps (NETs) formation and eventual kidney injury.

Methods: Control mice, mice treated with phorbol 12-myristate 13-acetate (PMA) to induce NETosis, and mice models of type 1 and type 2 diabetes treated either with Cl-aminide to inhibit NETosis or with Cl-aminide’s vehicle were used. Functional, histological, and molecular parameters of the kidneys were determined. Human transcriptomics datasets from GEO were further used for validation.

Results: Our data show that increased NETs formation mediates renal dysfunction and histopathological alterations associated with DKD. Of note, treatment with PMA mimicked diabetes-associated renal injury, as assessed by UAE, UACR, BUN and serum
cystatin C, and induced glomerular hypertrophy, glomerulosclerosis, extracellular matrix expansion, and interstitial fibrosis. Treatment with gliclazide limited blood glucose levels, decreased induced glomerular and podocyte injury. Increased NETs formation in diabetes was paralleled by an increase in NOX-dependent ROS production and mTOR signaling pathway activation. Our findings were further confirmed in transcriptomic analysis of glomerular tissue. A positive correlation between NETs and DKD was observed. Querying protein-protein interaction databases also revealed an association between NETs markers, mTOR signaling proteins, and NOXs.

Conclusions: To our knowledge, this study is the first to describe the role of NETosis in DKD, identifying NETosis as one of the final mechanistic drivers of DKD. NETs markers, mTOR signaling proteins, and NOXs paralleled by an increase in NOX-dependent ROS production and mTOR signaling induced glomerular and podocyte injury. Increased NETs formation in diabetes was associated with diabetes mellitus.

PO0679

Alteration of Autophagy-Related Protein 5 (ATG5) Levels and Atg5 Gene Expression in Diabetic Mellitus with and Without Complications

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Background: Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or ineffective intracellular components. Autophagy is the process responsible for normal cellular homeostasis, by recycling organelles and proteins. Autophagy pathway and its key participant ATG5 and LC3B were analyzed in both human model and murine tissues. One hundred and twenty human subjects were divided into four groups: Healthy (control), diabetic without complications, diabetic nephropathy and diabetic retinopathy. Additionally, we used kidneys from diabetic mice model (WT healthy mice and DM mice). Losses defined from human peripheral blood mononuclear cells, and murine renal cortex lysates were subjected to western blot analyses of ATG5 and LC3B and immunohistochemical analysis was performed on mice renal samples.

Results: Western blot and immunohistochemical analysis demonstrate that ATG5 protein levels were significantly decreased in DM, DN and DR patients (0.59±0.07; 0.67±0.06; 0.72±0.06 A.U. units respectively), vs. healthy controls (0.90±0.16 A.U. units), and in DN mice compared to healthy mice (0.65±0.04; 1.15±0.13 A.U. units respectively). Quantification of staining area (%) of ATG5 mice tissue expression also decreased in DN vs. healthy mice (4.42±1.08%; 10.87±1.01% respectively). LC3B levels and expression correlates with ATG5 results: significant reduction in peripheral blood mononuclear cells diabetic patients (with or without complications) vs. healthy controls (0.90±0.07; 0.59±0.06 A.U. units). Renal LC3B levels were lower in DN vs. healthy mice (0.60±0.03; 0.68±0.07 A.U. units). Renal LC3B staining quantification revealed significant reduction in DN vs. healthy mice (1.72±0.23%; 8.5±1.77%).

Conclusions: We conclude that ATG5, as well as LC3B, are down regulated in diabetic patients with or without complications. This diminution contributes to deficiencies in the autophagy process. Our observations show a novel association between autophagy-related protein 5 (ATG5) and diabetic kidney and retinal diseases, with ATG5 as a candidate protein for diabetic nephropathy and retinopathy.

PO0680

The Emerging Role of the mTORC2/Rictor Signaling Complex in Autophagy Dysregulation-Associated Diabetic Kidney Disease

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Background: Podocyte injury has been implicated in the pathogenesis of many renal diseases including diabetic kidney disease (DKD). Dysregulation of podocyte autophagy has been positively correlated with podocyte loss and progression of proteinuria in patients with diabetes. Yet, the exact mechanisms behind diabetes-induced autophagy dysfunction remain unidentified. Various signaling pathways including the mTORC1 complex have been implicated in modulating podocyte integrity. However, the role of mTORC2 in autophagy and its interaction with key mechanistic pathways involved in DKD, including the ROS-producing enzymes, are still unknown. Herein, we investigated the role of mTORC2, its crosstalk with the NADPH oxidases (NOXs), and its effect on autophagy, and the possible link to podocyte integrity in animal models of type 1 and type 2 diabetes.

Methods: Type1 diabetes was induced in mice by streptozotocin (STZ) injections, and type 2 diabetes was initiated by a ‘western’ diet followed by low-dose STZ injections. Mice were divided into control, diabetic, and diabetic treated with a selective mTORC2 inhibitor (JR-AB2-011). Functional, pathological, and biochemical studies were performed.

Results: Diabetes-induced podocyte injury is reflected by alterations of the slit diaphragm protein nephrin, paralleled by podocyte depletion as assessed by decreased WT1 staining and accompanied by autophagy dysregulation. The effect of autophagy was further highlighted in control mice treated with the autophagy inhibitor hydroxychloroquine, that mirrored the effect of diabetes on functional, phenotypic, histological, and molecular changes in the kidney. These observations were concomitant with an observed activation of the mTORC2/Rictor protein expression and increased levels of superoxide generation through NOX4. Of interest, these results were paralleled by activation of the mTORC1/p70S6K pathway. Moreover, specific inhibition of mTORC2 curbed the homeostatic function of the kidneys and restored the histological and pathological changes, consistent with regulating the Nox/mTORC1 signaling axis. More importantly, JR treatment regulated diabetes-induced autophagy protein dysregulation (Becn1, Atg3, and LC3).

Conclusions: Our data suggest that targeting mTORC2 signaling could be a potential therapeutic target for DKD.

PO0681

Mitophagy-Related Renal and Proximal Tubular Protection During the Normoammonuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the normoammonuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria. Because accumulation of damaged mitochondria can contribute to renal dysfunction, we aimed to determine a) if oxidative stress triggers mitophagy as a mitochondrial quality control mechanism, and b) the renal cortical structures in which these events occur.

Methods: Rats receiving i.p. injection of streptozotocin (STZ, 65 mg/kg) or vehicle (Sham) were either left untreated or treated with telmisartan (TLM, an angiotensin II receptor blocker; 10 mg/kg/d). Two weeks later, blood pressure (BP), glomerular filtration rate, and urinary excretion of albumin and N-acetyl-β-D-glucosaminidase (NAG) were measured. The oxidative stress marker, 3-nitrotyrosine (3-NT), was detected by HPLC. Mitophagy-related parameters (LC3-II, p62, PINK1) were quantified by western blot and localized by immunoreactivity based on percent of cells staining with various intensities (HistoScore).

Results: STZ rats displayed hyperglycemia and hyperfiltration that were unaffected by TLM. BP, albumin excretion, and NAG excretion were similar in all groups. Renal cortical 3-NT levels were increased in STZ rats, a change that was prevented by TLM (STZ+TLM). Renal cortex from STZ rats displayed TLM-sensitive increases in LC3-II and PINK1 (all P<0.05), although BNIP3 and p62 levels did not differ among groups. HistoScore data failed to reveal mitophagy-related proteins in glomeruli. In contrast, in the renal cortex, all mitophagy-related proteins were quantified by western blot and localized by immunoreactivity.

Conclusions: Mitophagy-related renal immunostaining was also apparent in distal tubules, but the HistoScores tended to be less than that of proximal tubules and were unaffected by STZ or TLM.

PO0682

The Molecular Effect of the Sodium-Glucose Transporter 2 (SGLT-2) Inhibitor Empagliflozin on the Autophagy Pathway in Diabetes Mellitus and Its Vascular Complications

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Background: Diabetes mellitus (DM) is a severe metabolic disorder characterized by chronic hyperglycemia. DM is associated with increased oxidative stress that can lead to irreversible kidney damage and vascular complications. Inhibiting the sodium-glucose transporter 2 (SGLT-2) with an oral antidiabetic drug, known as SGLT2i in T2DM patients. Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or dysfunctional intracellular components, and is known to have an important role in DM complication (Diabetic nephropathy-DN) and vascular disease. The protective role of EMPA treatment on DN via the autophagic proteins ATG5 & LC3B.

Methods: We used T2DM animal model-mouse strain BTBR with the ob/ob leptin-deficiency mutation that develops severe type II DM which is presented with hyperglycemia and DN. EMPA will be administrated to the diabetic mice via drinking water for a period of 12 weeks. Routine monitoring of blood and urine standard DM parameters will be carried through experiment duration. At the end of the experiment, mice kidneys will be removed and subjected to further biochemical and histological analysis. Intestinal and proximal tubular atrophy and interstitial fibrosis will be performed to evaluate ATG5, LC3B, level and expression.

Results: Blood glucose concentration was normal in control mice (C57) throughout the experiment. In DM mice (BTBR) without EMPA, blood glucose concentration was higher than control, and lower in diabetic mice treated with EMPA compared to DM. Urine volume of BTBR mice treated with EMPA increased throughout the experiment and was higher in comparison to DM mice without EMPA treatment. Renal cortical
expression of ATG5 were 6.83±0.52%, 2.59±0.34% and 6.29±0.74% for the C57, DM and DM-EMPA, respectively (P=0.001 vs. DM for both) and LC3B were 9.60±2.14%, 3.19±0.66% and 7.39±1.74% in the C57, DM mice and DM+EMPA, respectively (P<0.001 between all groups).

Conclusions: 1. EMPA Treatment induces glucosuria and body weight reduction in diabetic mice model. 2. Chronic Hyperglycemia down regulates the expression of LC3 & ATG5, the two main proteins in the autophagy process. 3. Treatment EMPA for 12 weeks restore the the expression of these proteins in the kidney.

PO0684
Ferroptosis Is Involved in the Process of Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is a major public health problem that threatens human health and causes substantial economic burden. DKD is accompanied by accumulation of ROS and iron in the kidney, a hallmark of ferroptosis. Ferroptosis is a condition that causes cell death by accumulation of lipid reactive oxygen species (ROS), in an iron-dependent mechanism that is different from apoptosis, necroptosis and autophagy. That ferroptosis is involved in DKD has been shown recently, but its role is still unknown.

Methods: We induced diabetic kidney disease in 8-week-old male rats with streptozotocin (STZ) and treated with ferroptosis inhibitor Fer-1 to analyze the degree of renal injury and the related indexes of ferroptosis.


Conclusions: Ferroptosis is involved in the process of diabetic kidney disease. Markers of renal tubular injury α1-microglobulin and N-acetyl-β-D-glucosaminidase measured in urine.

PO0685
miR299a-5p Is a Novel Mediator of Fibrosis in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses, mediated by the cytokines TGFβ1 and activins, plays a central role in its pathogenesis. We recently showed that TGFβ1 upregulation of microRNA(miR)299a-5p promoted its profibrotic responses in MC. Here we studied the role of this miR in DKD.

Methods: Primary mouse MC were treated with HG at 30 mM, miR299a-5p was detected by qPCR or ISH. miR overexpression and inhibition plasmids were transfected by electroporation. TGFβ1 and activin signaling was assessed by activity of their downstream mediator Smad3 using the CAGA reporter. ECM production was assessed using immunoblotting and activity of the COL1α1 promoter luciferase reporter.

Results: HG increased the expression of miR299a-5p in MC. This was also increased in type 1 Akita diabetic kidneys in both glomeruli and tubules, as assessed by ISH. In MC, miR299a-5p overexpression increased Smad3 activation and COL1α1 promoter activity. Conversely, miR299a-5p inhibition attenuated HG-induced COL1α1 promoter and Smad3 activation, as well as upregulation of ECM proteins. miR-299a-5p is predicted to target the TGFβ1 inhibitor Fst (FST). Here we show that HG decreased expression of both CR1 and FST. This was similar to seen with miR299a-5p overexpression. CR1 or FST treatment individually attenuated the increased COL1α1 promoter and Smad3 activity seen with miR299a-5p overexpression, and together showed an additive inhibitory effect.

Conclusions: These data support an important role for miR299a-5p in regulation of the profibrotic response to HG. Through suppression of two important anti-fibrotic proteins, CR-1 and FST, miR299a-5p potentiates the action of TGFβ1 family profibrotic cytokines. Future studies will determine whether inhibition of this miR can attenuate DKD.

Funding: Government Support - Non-U.S.

PO0686
Abstract Withdrawn

PO0687
The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical Diabetic CKD
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Background: The steroidal MR antagonist (MRA) spironolactone and eplerenone reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) but their use in patients with CKD is not indicated due to the associated risk of hyperkalemia. Finerenone is a non-steroidal MRA which recently reduced the composite kidney and cardiovascular outcomes in the phase III study FIDELIO in CKD patients with T2D. Purpose: To test whether finerenone improves renal and cardiac function in preclinical CKD rat models with T2D.

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247
Methods: 12 weeks old male Zucker Diabetic rats (ZSF1) were used as model of diabetes. The animals were administered with a dose of 10 mg/kg po, GFR (transcutaneous FITC-tisnitrin) and cardiac LV function/hemodynamics (LV catheterization) and LV tissue perfusion (MRI) were assessed in vivo at the age of 24 weeks.

Results: 24-week old ZSF1 rats showed classical signs of CKD, with reduced GFR (1.44±0.11 ml/min/100g body weight for non-diabetic rats vs 1.04±0.16 ml/min/100g body weight for ZSF1, p<0.05). This was associated with LV diastolic dysfunction, illustrated by an increase in LV end-diastolic pressure (LVEDP; 5.50±0.84 vs. 3.04±0.05), and LV end-diastolic pressure-volume relation (LVEDPVR; 1.0±0.23 vs. 5.63±0.54 mmHg/relative volume unit, p<0.05) without significant changes in LV end-systolic pressure (LVESP; 173±10 vs 197±5 mmHg) or LV end-systolic pressure-volume relation (LVESPVR; 37±4.2 vs 28.2±1.9 mmHg/relative volume unit; p<0.05). Finerenone treatment did not impact GFR in ZSF1 rats (0.93±0.17 ml/min/100g body weight) but reduced significantly LVEDP (5.72±0.76 mmHg, p<0.05) and LV end-diastolic pressure-volume relation (LVEDPVR; 2.73±0.33 mmHg/relative volume unit; p<0.05). Finerenone increased LV tissue perfusion (6.9±0.34 ml/min/g LV tissue).

Conclusions: Finerenone treatment improves CKD related LV diastolic function in diabetic CKD rats, independently from changes in GFR.

Funding: Commercial Support - Bayer Grant

PO0689

Development and Benchmarking of a Non-Human Primate Model of Diabetic Kidney Disease

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Background: Diabetic Kidney Disease (DKD) is the largest cause of end stage renal disease and is responsible for 40% of new patients that require dialysis. To test novel therapies for DKD, we sought to develop a non-human primate (NHP) model of DKD that would be more representative of the etiology of human disease than genetically modified mouse models and support human dose prediction and biomarker development.

Methods: Monkeys were fed a high fat/cholesterol diet for 5.1±2.5 (mean±SD) years and became obese (9.1±1.6 kg), hyperglycemic (267±78 mg/dL), hypertensive (141±11 mmHg), and macroalbuminuric (urine albumin/creatinine ratio [UACR] 562±346 mg/g). The responsiveness of the monkeys to pharmacological intervention was benchmarked using irbesartan, an angiotensin II receptor blocker (ARB), which is used in human DKD. Animals were orally dosed daily for 8 weeks with either vehicle (n=8) or irbesartan (n=13, 4.3 mg/kg).

Results: Exposures 24-hours after dosing were 165±111 ng/mL, similar to exposure in humans with therapeutic concentrations. Treatment with irbesartan (28.5±5.5, 77.5±12.5, 131±20.5, 185±23.2, 360±78.5, 540±123, 720±151.5, 1080±223.7 ng/mL) increased UACR in all groups (vehicle 156±38, irbesartan 562±346 mg/g).

Conclusions: Together, these data demonstrate that we have developed and benchmarked a novel NHP model for DKD that has characteristics similar to human pathology and response to treatment known to improve outcomes. This model is expected to be a valuable translational model for testing novel interventions for DKD.

Funding: Commercial Support - Janssen Pharmaceutical Companies of Johnson and Johnson

PO0690

Insulin Receptor Signaling Is Necessary for NFXB-Activated Host Defense Responses in Murine Intercalated Cells

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Background: Urinary tract infection (UTI) disproportionately affects select groups, especially those with insulin resistance and diabetic mellitus. Intercalated cells (IC) play a key role in preventing UTI by regulating urine pH and secreting cytokines and antimicrobial peptides (AMP). Our data show that insulin receptor (IR) deletion in murine IC causes insulin resistance and increases UTI risk in vivo while having no impact on glucose homeostasis or urine acidification. Here, we profile the transcriptomes of IC isolated from IR knockout (IRKO) mice and controls (WT) to identify IR-mediated host defenses.

Methods: Intergra gene was deleted in murine IC by breeding Atp6v0d2-Cre transgenic mice with IR-Flox mice. A tdT reporter was added to aid fluorescence-activated cell sorting (FACS) of IC. RNAseq was performed on IC and read count data were analyzed for differentially expressed genes (DEG) using edgeR. DEG were defined with FDR adjusted p-value < 0.05. Canonical pathway analysis of DEG was performed using Ingenuity Pathway Analysis. Sorted IC were cultured and challenged in vitro with uraporphagic E.coli (UEPC) to assess response and susceptibility to infection. To define the contributions of NFXB to UTI defense, NFKB1 was silenced in humanened cells using siRNA. UPEC attachment and invasion assays were performed.

Results: FACSEnriched IC express IC-specific genes like Agp6 and Apo6/02. Differential analysis reveals suppression of 138 genes and upregulation of 232 genes in IRKO vs WT IC. In IRKO IC, a decrease in Infr as well as downstream IR-regulated targets and host defense genes such as AMPs were observed. While diverse pathways implicated in innate immunity are suppressed in IRKO IC, many converge on mTOR signaling. When cultured with these stimuli, human IC from NFKB1 KO IC exhibit suppressed Nfkb activation and UPEC were more likely to invade them. Silencing NFKB1 results in decreased AMP expression and increased UPEC attachment and invasion of humanimal cells.

Conclusions: In murine IC, IR signaling impacts the IC host defense transcriptome and identifies IR-sensitive pathways that aid in UPEC defense by activating NFKB signaling and expressing AMPs. A greater understanding of the factors that predispose diabetics to UTI may reveal novel, targeted therapies to prevent/treat diabetes-associated UTI.

Funding: NIDDK Support

PO0691

The HIV Protease Inhibitor Darunavir Protects Against Diabetic Kidney Injury in Mice and Alters Stress Granule-Associated Signaling

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Background: Despite the success of antiretroviral therapy (ART) in improving mortality, persons living with HIV (PLWH) still have increased risk of death and kidney disease and diabetes mellitus are important contributors to this excess mortality. Previously we demonstrated that the protease inhibitor darunavir (DRV) protects against renal injury in the 5/6 nephrectomy and adriamycin models of nephropathy, and our expression in mesangial cells has been proposed to contribute to kidney pathology through regulation of matrix production. We assessed the contribution of eNOS protein to human DKD kidney and in multiple preclinical species to better understand the role of the cell type responsible.

Methods: Humans kidney from normal and DKD subjects, as well as kidneys from diabetic mice, rats and cynomolgus monkeys were evaluated by immunohistochemistry (IHC) for eNOS expression. Staining antibody was validated with kidneys from o2-KO mice. Identification of eNOS-positive cell types and scoring was performed by a trained pathologist. Protein expression was compared with RNA expression in mRNAseq datasets from human DKD kidneys and kidneys from db/db mice.

Results: All species showed strong staining in the medulla, but significant differences were noted in the cortical o2 expression between humans and other species. Mainly mesangial, endothelial and distal tubular staining was seen in human DKD. Podocytes were negative while proximal tubules stained weakly. Consistent with IHC data, strong o2 expression in human distal tubules and weaker expression in proximal tubules and glomerular cell types is seen in mRNAseq data. In contrast, mice showed mainly podocyte and endothelial staining. Mesangial cells and proximal tubules were negative for o2, and distal tubules in the cortex stained weakly. Rat kidneys were negative for glomerular o2 expression with medium to strong positivity in the distal tubules of the cortex. Finally, cynomolgus monkeys showed o2 expression in all glomerular cell types: podocytes, endothelial and mesangial, weak staining in proximal and medium to strong staining in distal tubules. Decreased o2 glomerular staining was observed in DKD kidneys compared to normal kidneys.

Conclusions: Differences in o2 expression pattern must be considered when extrapolating from lower to higher species.

Funding: Commercial Support - Jansen
Srivastava, and Erd were increased in the kidneys of diabetic eNOS--/ mice and these changes were reduced by BHB treatment. To directly test the role of G3BP1 in promoting Stat3, Srrc, and Erd phosphorylation, we used siRNA to knockdown G3BP1 expression in human tubular cells, which reduced phosphorylation of Stat3, Srrc, and Erd.

**Conclusions:** These data suggest that DRV prevents diabetes-induced kidney injury in mice in part, via interactions with the SG protein G3BP1. Additional studies are needed to further delineate the effects of targeting SG function upon diabetic kidney injury.

**Funding:** NIDDK Support

**PO0692**

The Role of Intestinal Flora in Cinnamaldehyde Alleviating Early Diabetic Kidney Disease: Basic - II

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**Background:** Intestinal dysbiosis played a crucial role in chronic inflammation of diabetic nephropathy (DN). Cinnamaldehyde (CIN) is a traditional natural food additive from a Chinese herb, recognized as an antidiabetic and antibacterial medicine recently. This study was to observe the effects of CIN on renal injury and intestinal flora in DN.

**Methods:** A total of four groups of rats included DN group induced by streptozotocin (70mg/kg), treated with CIN (DNC), control (NC), and NC treated with CIN (NCC). CIN was given daily for 8 weeks. Blood glucose, bodyweight, 24h urinary volume (24hV), protein (24hUP), the pathology changes of kidney, and the protein expression of Megalin, Fibronectin, TGF-β were measured. We also sequenced 16S rDNA of the intestinal flora of the rats.

**Results:** Compared with DN, DNC showed significant improvement with lower 24hV, decreased Fibronectin, TGF-β, and increased Megalin. Simpson's diversity index of the intestinal flora significantly decreased in the DNC group. PCoA (Fig. A) showed different patterns of clustering between the 4 groups (p<0.01). At genera, compared with NC, g. _Lactobacillus_ decreased significantly in DN, but recovered in DNC, and was also confirmed as significant biomarkers by LEfSe (Fig. B). Besides _Lactobacillus_, there were 12 other differentially enriched genera in DNC, such as g. _Alloprevotella_, and g. _Oscillibacter_. At species, 3 species decreased in DN and recovered in DNC, including _s. Bacteroides maxilimus_, s. _Oscillibacter SP_E4_, and s. _Lachnospiraceae bacterium A2_. They were anti-inflammatory probiotics that produce short-chain fatty acids. The abundance of 6 genera correlated well with 24hUP (p<0.05, Fig.C). Tax4fun (Fig.D) showed significant differentially enriched functional categories.

**Conclusions:** Cinnamaldehyde could alleviate renal injury in DN, which was associated with the recovery of the reduced intestinal g. _Lactobacillus_.

PO0693

Hypercglycemia-Induced Mitochondrial Dysfunction in Kidney and Brain Are Protected by β-Hydroxybutyrate Treatment

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**Background:** The immediate effects of hyperglycemia on mitochondrial and organ dysfunction are poorly understood. Acute hyperglycemia could reveal key initiating events to determine how organ dysfunction ensues, particularly in response to repeated hyperglycemia exposures as occurs with poorly controlled diabetes. The potential protective benefit of ketone bodies on mitochondrial function across organs during hyperglycemia has also not been well characterized. Here, we evaluated effects of hyperglycemia and β-hydroxybutyrate (BHB) on ATP production in the mouse using a novel in vivo brain imaging approach in combination with MALDI-MSI.

**Methods:** GFP-Ii-LacIIe-dual-glo transgenic mice were used to test the effect of BHB on brain luciferin-luciferase bioluminescence using a Xenogen IVIS spectrum live-imaging system. Transgenic dual-glo mice expressed the luciferase in astrocytes under the gfp promoter. MALDI-MSI analysis was used to detect the acute impact of BHB on small molecule metabolites in the kidneys and brains of C57BL/6J mice. For in vivo imaging, either 2.5 g/kg of BHB, 2 g/kg of glucose, or 25 mM glucose with MALDI-MSI. BHB treatments increased ATP levels in the brain and kidney tissues and cells. Acute glucose exposure in HK2 cells reduced OCR and increased ECAR, which was blocked by BHB treatment. In contrast, brain bioluminescence was significantly decreased when mice were injected with 25 mM glucose (4 minutes after luciferin injection), consistent with a loss in ATP production. In contrast BHB injections increased bioluminescence and blocked the loss of signal in the presence of high glucose.

**Conclusions:** These data indicate that acute glucose exposure reduces ATP production in the kidney and brain, and that BHB can reverse this effect. Together, these studies suggest the acute detrimental effects of hyperglycemia on metabolism and mitochondrial dysfunction can be reversed with ketone bodies treatment.

**Funding:** Private Foundation Support

**PO0694**

Dysfunction of the Renal Tubular Circadian Clock Leads to Enhanced Renal Gluconeogenesis and Exacerbated Hyperglycemia in Diabetics

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**Background:** The circadian rhythms define all biological process cycling with a periodicity of about 24 hours. They are believed to be an evolutionary adaptation that allows biological functions to anticipate variations of environmental conditions imposed by Earth's cycles. These rhythms are driven by the circadian clock, a molecular system of interconnecting loops present in virtually each cell of the body. Disruption of the circadian rhythms or its misalignment with external environment is a risk factor for development of numerous diseases, such as depression, obesity, diabetes or cancers. However, the pathophysiological role of intrinsic renal circadian clocks in the diabetic kidney remains unknown.

**Methods:** To address this question, we used mice with streptozotocin-induced type I diabetes, and carrying Bmal1 deletion either in the podocytes (pCKO mice) or in whole renal tubular cells (eCKO mice).

**Results:** Although diabetic pCKO mice did not show any additional alterations compared to diabetic Control mice, diabetic eCKO mice showed exacerbated hyperglycemia, increased fractional excretion of glucose, enhanced polyclonia and a more severe renal hypertrophy, compared to diabetic Control mice. Interestingly, renal gluconeogenic pathway was enhanced in diabetic eCKO mice, as demonstrated by increased protein and mRNA expression levels of key enzymes. Moreover, deep sequencing transcriptome and functional analysis of diabetic eCKO mice showed alterations in several mechanisms affecting the gluconeogenic pathway.

**Conclusions:** Altogether, our data demonstrate that disturbance of renal tubular circadian clock enhances gluconeogenesis in proximal tubule, leading to the aggravation of the hyperglycemia of diabetic mice. These results highlight importance of circadian behaviour in diabetic patients.

**Funding:** Other NIH Support - Swiss National Science Foundation (SNF)

**PO0695**

Dysregulation of Thiosulfate Thiotransferase Pathway Contributes to Tubulointerstitial Injury of Diabetic Nephropathy

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**Background:** Tubulointerstitial injury plays an important role in the progression of diabetic nephropathy (DN), and its severity is closely related to the prognosis of DN. Thiosulfate thiotransferase (TST) is a key enzyme that mediates protein S-sulfhydrylation and maintains mitochondrial metabolic homeostasis. This study aimed to investigate the role of TST in tubulointerstitial injury of DN and to explore its potential mechanisms.

**Methods:** Sodium thiosulfate (STS)-treated diabetic mice, adeno-associated virus with TST overexpression transfected diabetic mice, and cell culture model of HK-2 cells transfected by lentivirus with TST overexpression were used for experiments. The protein S-sulfhydrylation of very long-chain acyl-CoA dehydrogenase (VLCAD) was checked by Western blotting and mass spectrometry analysis. Tubular mitochondrial mitochondrial fatty acid β oxidation (FAO) was checked by 13C labeling combined with mass spectrometry and Seahorse assay. Epithelial mesenchymal transition (EMT) related molecules of tubular epithelial cells were checked by immunofluorescent staining and Western blotting.

**Results:** Our results showed that the expression of TST was decreased in kidneys of diabetic mice and in high glucose-stimulated HK-2 cells, which was significantly correlated with decreased E-cadherin and increased protein expression of collagen I, fibronectin, and α-SMA. Furthermore, the down-regulation of TST expression led to the FAO dysfunction in kidneys of diabetic mice and in high glucose-stimulated HK-cells. On the contrary, STS treatment or overexpression of TST alleviated albuminuria and tubulointerstitial injury. The expression of collagen I, fibronectin, and α-SMA in TST transfected diabetic mice or HK-2 cells were significantly decreased, while E-cadherin expression was increased. Further analysis showed that pharmacological inhibition of STS

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249
or overexpression of TST improved mitochondrial FAO dysfunction and tubulointerstitial injury in diabetic mice and in high glucose-stimulated HK-2 cells, which was mainly through the increased S-sulfhydrylation modification of VCLAD.

**Conclusions:** These findings demonstrated that down-regulation of TST expression mediated the decrease of S-sulfhydrylation modification of VCLAD, which led to mitochondrial FAO dysfunction and then exacerbated the progression of tubulointerstitial injury in DN.

**PO0696**

**CYP450: Protagonists in the Story of Diabetic Kidney Disease**

**Batoul Dia, Mohamed Noureldeen, Sami Azar, Faud N. Ziyadeh, Assaad Antonio Eid. American University of Beirut, Beirut, Lebanon**

**Background:** Diabetic kidney disease (DKD) is a grave complication and a major contributor to patient mortality in patients with diabetes. Cytochrome P450 (CYPs) epoxide hydrolases metabolize arachidonic acid into the vasoactive and renal-active HETEs and EETs. Our group, among others, advanced the discovery implicating CYPs and their metabolites in the pathogenesis of DKD by regulating reactive oxygen species. Of interest, CYPs encoding genes possess different polymorphisms which alter the expression of these key enzymes, affecting the prognosis of patients with DKD. Noteworthy, the CYPs polymorphisms and their correlation with the production of 20-HETE and EETs in DKD remain poorly investigated. In the same spirit, extensive research has highlighted the role of different mRNAs in DKD. To our knowledge, the regulatory effect of mRNAs on the expression of different CYPs in DKD is not yet established. In this study, we aim to elucidate the role of CYPs polymorphism, their metabolites, and miRNAs regulating their expression in the disease onset and progression of DKD.

**Methods:** Blood and kidney tissues were collected from patients with type 2 diabetes (T2D) with or without clinical manifestation of DKD. Levels of 20-HETE and EETs were measured in the serum of the patients and we investigated the association of these metabolites with different CYPs in diabetic kidneys. Besides, miRNA analysis was performed on the plasma obtained from these patients to study CYP enzymes regulation using the TargetScan online tool.

**Results:** Our data show that the circulating levels of 11,12-EETs were decreased in patients with DKD when compared to T2D patients with no clinical signs of DKD, concomitant with an increase in the 20-HETE levels. Our results show that in patients with DKD, the expression of miRNA was altered ultimately leading to the downregulation of CYP2B6, CYP4A11 and CYP4F8 enzymes. Furthermore, patients with DKD carry CYP polymorph with the minor allele frequency resulting in an alteration in their enzymatic activity and subsequently increasing 20-HETE, decreasing D6-desaturation of PUFAs, concomitant with a positive correlation with the expression of the corresponding CYPs in human kidney biopsies.

**Conclusions:** This study yields crucial findings about novel genetic and epigenetic pathways involved in the initiation and progression of-DKD related to CYPs pathways that could be of diagnostic, prognostic, and therapeutic value.

**Funding:** Private Foundation Support, Clinical Revenue Support

**PO0697**

**Metabolic Images Using Fluorescence Lifetime Imaging Reveals Metabolic Alteration in Proximal Tubular Epithelial Cells in Type 2 Diabetes**

**Woo Young Kwon,1 Gun Tae Jung,2 Su Woong Jung,1 Yang gyun Kim,1 Sangho Lee,1 Kwang Pyo Kim,2,1 Weon-Sik Chea,2 Ju young Moon.1 Division of Nephrology, Department of Internal Medicine, Kyung Hee University, College of Medicine, Seoul, Republic of Korea; 1Department of Biomedical Science and Technology, Kyung Hee Medical Science Research Institute, Kyung Hee University, Seoul, Republic of Korea; 2Department of Applied Chemistry, Institute of Natural Science, Global Center for Pharmaceutical Ingredient Materials, Kyung Hee University, Yongin, Republic of Korea; 3Daegu Center, Korea Basic Science Institute, Daegu, Republic of Korea.**

**Background:** Although there is a massive metabolic alteration of the kidney in diabetes, it is difficult to detect and measure the single-cell nicotinamide adenine dinucleotide hydrogen (NADH), flavin adenine dinucleotide (FAD) production, and redox potential. In particular, proximal tubular epithelial cells (PTECs) are the most labile cells and affected cells under high glucose environments. We investigated this study to evaluate quantitative PTECs-specific metabolic images in the diabetic kidney using fluorescence lifetime imaging (FLIM).

**Methods:** Kidney sections of 20 week-old db/db and db/m mice were used for FLIM. FLIM images are analyzed using the phasor approach. The FLIM image and phasor plot representing FLIM data in vector space were measured through Leica TCS SP8 SMD and LAS-X software. The NADH, FAD, and ATP levels in diabetic kidneys were measured using LC-MS analysis by Q-trap 5500.

**Results:** NADH and FAD located at the different subcellular levels in PTECs. The NADH phasor analysis of PTECs revealed a right-ward shift toward shorter lifetimes from the db/m to the db/db, while there was no significant alteration of FAD between the two groups. It could be indicative of an increase in the NADH-to-FAD ratio that alters metabolic flux. In addition, the levels of NADH in diabetic kidneys were significantly increased than db/m, while the levels of FAD were reduced in diabetic kidneys. Finally, ATP level decreased in the diabetic kidney compared to db/m.

**Conclusions:** FLIM enables an alternative approach to characterize and monitor metabolism in diabetic kidneys. Quantitative metabolic imaging using FLIM enables to measure and analyze metabolic alteration with spatial information.

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**PO0698**

**Female Protection Against Diabetes-Induced Kidney Injury Is Eliminated in Kidney Tubule-Specific AMPK Gamma-2 Knockout Mice**

**Li, Jin, Jingli Gao,1 Hak Joo Lee,1 Guoguo Xu,1 Goutam Ghosh-Choudhury,2,1 Balkakantalam S. Kasinath,1,3 Kumar Sharma,1,2 The University of Texas Health Science Center at San Antonio, San Antonio, TX; South Texas Veterans Health Care System, San Antonio, TX.**

**Background:** Reduction in renal AMPK activity is associated with obesity- and diabetes-induced kidney injury which is ameliorated by AMPK stimulation in male mice. Female mice resist obesity-induced kidney injury; this protection is abolished in kidney tubule specific c1 and c2 KO female mice. We tested if interruption of AMPK activity abrogates renal protection against diabetes in AMPK c2 KO female mice. We also tested if diabetes worsens kidney injury in AMPK c2 KO male mice.

**Methods:** We used 14 month-old tubule-specific AMPK c2 KO male and female mice (n = 6-9 per group) were employed. To generate diabetic animal model, the mice were placed on a high fat diet (HFD) for one month, then they received streptozotocin (STZ) 50mg/kg body weight by IP daily for 5 days. After one month STZ injection, urine was collected for analyzing urinary KIM-1 and ACR.

**Results:** Renal cortical expression of AMPK c2 mRNA as well as protein was reduced in AMPK c2 KO mice. There were no changes in body weight and random blood glucose levels between control and AMPK c2 KO male and female mice at the baseline. Body weight gain in control and AMPK c2 KO mice in both genders was increased by HFD compared to normal diet fed groups. Random blood glucose levels increased in HFD and STZ-treated control and AMPK c2 KO mice in both genders. As expected control female mice resisted HFD and STZ-induced kidney injury, whereas urinary KIM-1 and albuminuria were increased in AMPK c2 KO female mice. Urinary KIM-1 excretion and albuminuria were induced by diabetes in control and c2 KO male mice with no statistical difference between two groups.

**Conclusions:** Renal protection against diabetes is abolished in kidney tubule specific AMPK c2 KO female mice. Therefore, regulation of AMPK, as well as its activity contributes to the protective mechanism against diabetes in female mice, and it could be used for a therapeutic target of diabetes.

**PO0699**

**Mitochondrial Fission and Fusion Dynamics Are Regulated by Multiple Pathways in Renal Proximal Tubule Cells Treated with High Glucose**

**Kristian H. Cleveland, Rick G. Schnellmann. The University of Arizona, Tucson, AZ.**

**Background:** In type 2 diabetes, hyperglycemia leads to proximal tubular dysfunction, which is accompanied by altered mitochondrial homeostasis. We previously demonstrated that in renal proximal tubule cells (RPTC) grown in high glucose, as well as in diabetic db/db mice, mitochondrial dynamics were altered. Phosphorylation of the mitochondrial fission protein Drp1 increased and the mitochondrial fusion protein Mfn1 decreased. Studies have shown that Drp1 is activated by the RhoA/ROCK1 signaling cascade in the presence of high glucose, leading to increased mitochondrial fission. Conversely, Mfn1 can be activated by MEK/ERK signaling. However, these key enzymes, affecting the prognosis of patients with DKD have not been investigated in the proximal tubule. Therefore, we determined the signaling pathways responsible for altered Drp1 phosphorylation and Mfn1 expression in RPTC.

**Methods:** Primary cultures of RPTC were grown in the presence of high glucose (17mM), mannitol (17mM) or no glucose for 96h and were co-treated with either Rhoa (CCR1423), ROCK1 (Y27632) or MEK 1/2 (GSK 1120212) inhibitors 24h prior harvesting. Cells were subjected to GTPase assays to measure Drp1, Rhoa and Mfn1 activity and maximal mitochondrial respiration was measured using Seahorse XF96e analyzer.

**Results:** RPTC treated with glucose for 96h or exhibited an increase in Rhoa and pDrp1 at 96 h. This increase corresponded with an increase in GFP-bound Rhoa and Drp1. Co-treatment with CCR1423 or Y27632 prevented the glucose-induced increase in Rhoa and Drp1, respectively. Inhibition of Rhoa and ROCK1 restored maximal mitochondrial respiration. Co-treatment with GSK 1120212 prevented the glucose-induced decrease in Mfn1.

**Conclusions:** Together, these results demonstrate that treatment of RPTC with glucose increases Rhoa and Drp1 activity and maximal respiration. Pharmacological inhibition of Rhoa and ROCK1 prevented increased activity of Rhoa and Drp1 and restored respiration, indicating that the Rhoa/ROCK1/Drp1 signaling pathway is responsible for increased mitochondrial fission and respiration in high glucose in RPTC. In contrast, we show that inhibition of the MEK/ERK signaling cascade prevents the decrease in Mfn1 observed in the presence of high glucose. These data indicate that the alteration of mitochondrial dynamics in high glucose in RPTC, are regulated by two independent signaling pathways.

**Funding:** Veterans Affairs Support
**PO0700**

Medications Targeting the Activation of Tubular Fatty Acid Oxidation Enhance the Renoprotective Effects of Roux-en-Y Gastric Bypass Surgery

**Background:**

Roux-en-Y gastric bypass surgery (RYGB) improves biochemical and histological parameters of diabetic kidney disease (DKD). Targeted adjunct medical therapy may enhance renoprotection following RYGB.

**Methods:**

The effects of RYGB (n=10) and RYGB plus fenofibrate 100mg/kg, metformin 300mg/kg, ramipril 1mg/kg, and rosuvastatin 10mg/kg (RYGB-FMR; n=9) on metabolic control and histological and ultrastructural indices of renal injury were compared after 8 weeks of treatment in the Zucker Diabetic Sprague Dawley (ZDSD) rat model of DKD. Sham-operated ZDSD rats (n=9) and healthy Sprague Dawley rats (n=6) served as controls. Renal cortical transcriptomic (RNA-sequencing) and urinary metabolomic (1H-NMR spectroscopy) responses were profiled and integrated. Omic correlates of improvements in structural and ultrastructural indices of renal injury were defined using a molecular morphometric approach.

**Results:**

RYGB-FMR was superior to RYGB alone with respect to metabolic control, albuminuria, and histological and ultrastructural indices of glomerular injury. RYGB-FMR reversed DKD-associated changes in mitochondrial morphology in the proximal tubule to a greater extent than RYGB. Attenuation of transcriptomic pathway activation of pro-fibrotic responses was greater after RYGB-FMR than RYGB. Transcriptional induction of PPARα-regulated genes, expressed in the proximal tubule and governing fatty acid oxidation (FAO), was a unique feature of the RYGB-FMR transcriptome associated with increased urinary PPARα-responsive nictinamide metabolites and reduced urinary tricarboxylic acid (TCA) cycle intermediates. Multi-omics integration identified a strongly positively correlated network of FAO transcripts and metabolites as being distinctive to RYGB-FMR. Changes in FAO transcripts, nictinamide metabolites, and TCA cycle intermediates correlated strongly with improvements in global and proximal tubular injury followed by RYGB-FMR.

**Conclusions:**

The renoprotective effects of RYGB can be enhanced through the deployment of medications targeting PPARα-mediated activation of tubular FAO responses.

**Funding:**

Government Support - Non-U.S.

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**PO0701**

Polyamine Catabolism Is Enhanced in Streptozotocin-Treated Mice and in Cultured Proximal Tubule Cells Exposed to High Glucose Levels: A Possible Role in Tubular Injury in Diabetic Nephropathy

**Background:**

Polyamines are indispensable to cell growth and survival. Their cellular levels are regulated via import, export and metabolism. Their catabolism is mediated via the activities of spermine oxidase (SMOX) and spermine-spermidine-N1-acetyltransferase (SAT1)Acetylpyridoxamine oxidase (PAOX) cascade. Enhanced polyamine catabolism mediates cellular injury by induction of DNA and mitochondrial damage, activation of the endoplasmic reticulum stress/unfolded protein response (ERS/UPR) pathway, and innate immunity. Studies indicate that mitochondrial dysfunction, innate immune response and ERS/UPR are important mediators of tubular injury in diabetic nephropathy. We posit that polyamine catabolism is activated in diabetic mellitus and plays an important role in tubular injury.

**Methods:**

The expression of polyamine catabolic enzymes was examined in streptozotocin (STZ)-induced diabetes in mice and HK-2 proximal tubule cells exposed to high glucose (30mM) levels. The expression levels of SAT1 and SMOX were determined by northern and western blot analyses. Nephron segment expression and localization of SAT1 and SMOX in STZ-treated mice was determined by immunohistochemistry and immunofluorescence microscopy.

**Results:**

Expression of SAT1 and SMOX were elevated in the kidneys of STZ-treated mice compared to their vehicle-treated counterparts. Immunohistochemical and immunofluorescence microscopic studies revealed that SAT1 and SMOX expression are increased in the proximal tubule, distal convoluted tubule and collecting duct epithelial cells in vivo. In vitro studies using HK-2 cells demonstrated that the expression of both SAT1 and SMOX increases in relation to glucose exposure to 30mM glucose.

**Conclusions:**

Expression of polyamine catabolic enzymes, SAT1 and SMOX, is increased in proximal tubules, distal convoluted tubules and collecting ducts of mice with diabetes mellitus. Similarly, exposure of HK-2 cells to 30mM glucose increased the expression of both SAT1 and SMOX. Based on these studies and their known injurious effects, we propose that SAT1 and SMOX play a significant role in the mediation of renal injury in diabetes mellitus likely through the induction of oxidative injury, mitochondrial damage, elevated ERS/UPR and activation of innate immune responses.

**Funding:**

Veterans Affairs Support, Private Foundation Support

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**PO0702**

An Interplay of Glucose, IL-1β, and PDGF-B Trigger CPLA2 Activation, Prostaglandin Secretion, and Proliferation in Human Mesangial Cells

**Background:**

Diabetic kidney disease (DKD) is commonly thought to be originated from diabetic hyperglycemia. DKD development is driven by early glomerular hemodynamic changes and characterized by progressive expansion of the mesangium. A connection between these findings is yet to be elucidated. We speculate that, after hyperglycemia priming, autocrine inflammatory and proliferative stimuli alter mesangial lipid metabolism activating the secretion of vasodilator hormones. Subsequently, this affects glomerular functions. Phospholipase cPLA2 was identified as the central enzyme of the metabolic cascade.

**Methods:**

Human mesangial cells were stimulated with Glucose (30 mM), IL-1β (1 nm), PDGF-B (25 ng/ml). Their synergistic counter activation was investigated by western blots and qPCR. Lipidomics was used to analyze lipid variations. Cos 2 induction and prostaglandin secretion were measured via western blot and ELISA. Activation of cPLA2, upstream of Cox-2, was studied using western blot, qPCR, activity assays. ELISA, migration, and proliferation assays were used to evaluate cPLA2 inhibition. Data were validated using the Nephroeq database.

**Results:**

After stimulation with Glucose, NLRP3 and pro-IL-1β were upregulated. IL-1β stimulation increased PDGF-B mRNA levels. In turn, PDGF-B stimulation increased NLRP3 and pro-IL-1β protein levels. Lipidomics analysis after IL-1β and PDGF-B stimulations showed an increase of sphingosine 1 phosphate, a known activator of Cox-2. Cox-2 was induced and prostaglandins secreted accordingly. cPLA2 releases arachidonic acid, the substrate of Cox-2. cPLA2 was upregulated at gene and protein level and activated by phosphorylation. Upregulation of the pathway was confirmed in silico in DKD patients. Since cPLA2 reaction is the rate-limiting step in prostaglandin synthesis, its inhibition with ACOCCF3 was studied. Inhibition of cPLA2 reduced migration, proliferation, secretion of prostaglandins in cells treated with IL-1β and PDGF-B.

**Conclusions:**

External stimuli (hyperglycemia from the diabetic environment) and glomerular inflammatory and proliferative stimuli prime DKD early events. The upregulation of cPLA2 was found to be critical in these events. cPLA2 inhibition reduced mesangial secretion of prostaglandins, proliferation, and migration, making it a potential target for therapy.

**Funding:**

Private Foundation Support, Government Support - Non-U.S.
**Suppression of Endoplasmic Reticulum-Associated Degradation Process by Intraglomerular Cross-Talk Between Podocytes and Mesangial Cells Causes Podocyte Injury in Diabetic Kidney Disease**

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**Background:** Mesangial lesion and podocyte injury are essential for the progression of diabetic kidney disease (DKD). Although crosstalk between mesangial cells (MCs) and podocytes is recently suggested by single nucleus RNA-sequence analyses, its molecular mechanisms and role in disease progression still remain elusive.

**Methods:** We evaluated the ER stress responses of podocytes stimulated with mesangial cell conditioned culture medium (MC-sup) under high-glucose condition (HG) in vitro. Then, the effects of an ER-associated protein degradation (ERAD) inhibitor, yeastaratin 1 (Ieef1) in cultured podocytes and glomeruli of db/db (type 2 diabetic) mice were also examined by western blotting, immunofluorescence and TUNEL staining. Furthermore, we evaluated the effects of ERAD inhibitor on nephrin phosphorylation of podocytes by flowcytometric analysis and western blotting.

**Results:** In vitro experiments revealed the suppression of the ER-associated degradation (ERAD) pathway and induction of apoptosis in podocytes that were stimulated with the supernatant of mesangial cells cultured in high glucose conditions. In diabetic mice, ERAD inhibition resulted in exacerbated albuminuria, increased apoptosis in podocytes, and reduced nephrin expression associated with the downregulation of ERAD-related biomolecules. Flowcytometry analysis of podocytes isolated from db/db (a transcription factor known to be expressed in macrophages and podocytes) -GFP knock-in mice revealed that ERAD inhibition resulted in decreased nephrin phosphorylation. Decreased nephrin phosphorylation was also confirmed in in vitro experiments.

**Conclusions:** ERAD process has been reported to be important for avoiding ER stress and cellular damages. Our findings suggest that an intraglomerular crosstalk between MCs and podocytes inhibit physiology and ERAD processes and reduce phosphorylation of nephrin in podocytes, which thereby lead to podocyte injury under diabetic conditions. Therapeutic intervention of the ERAD pathway through the crosstalk between these cells is potentially a novel strategy for DKD.

**DPP4 Inhibitors Ameliorate Endoplasmic Reticulum Stress in Diabetic Kidney Disease Through Upregulation of SIRT1**

Qunzi Zhang, Ying Fan, Niansong Wang. Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai, China.

**Background:** Endoplasmic Reticulum (ER) stress plays vital roles in the progression of diabetic kidney disease (DKD), and Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used antihyperglycemic agents. Further exercising renal beneficial effects in DKD, but the precise mechanism underlying the disruption of these processes remains unclear. We examined whether SIRT1/STAT3 pathway regulated ER stress in the progression of DKD.

**Methods:** In vivo, male DBA2J mice were injected by streptozotocin to form diabetic mice models, then sitaglipitin(Sita) was gavaged to inhibit DPP4. We collected and analyzed kidney samples, urine and serum.

**Results:** ER stress were observed both in diabetic mice and in HSA-induced human HK-2 cells, as reflected by notably increased GRP78, CHOP, highly phosphorylated of PERK (p-PERK) and elevated cleaved caspase-3 (c-CASP3), whereas Sita effectively reduced both in vitro.

**Conclusions:** Our study presented that Sita can decrease ER stress in the progression of DN, and SIRT1 has a protective effect on diabetic ER homeostasis, whereas calcium unipporter (MCU) were examined through Western blot and immunohistochemistry in kidneys of STZ-induced diabetic and high glucose stimulated HK-2 cells. Calcium concentration in cells and mitochondria was detected through specific ELISA kit.

**Results:** In this study, upregulation of Wnt5a, increase of both cellular and mitochondrial Ca2+, mitochondrial fragmentation and altered mitochondrial dynamics-expression of some genes were detected in the tubules of diabetic mice and in high glucose stimulated HK-2 cells. In vitro, Wnt5a overexpression induced the Ca2+ influx and aggravated mitochondrial fusion-fission disorder. After amlopidine treatment, this Wnt5a-Ca2+ pathway was restored, mitochondrial dynamics and morphological changes were recovered. Additionally, increase of MCU was also observed in the mitochondrial of tubular cells in DN, suggesting a possible link between Wnt5a-Ca2+ pathway and mitochondrial dysfunction.

**Conclusions:** Our study presented that Wnt5a-Ca2+ signaling pathway might be involved in mitochondrial dysfunction in the progression of DN, and MCU was possibly recognized as the important link during the regulation.

**The Renoprotective Effects of the Soluble Guanylate Cyclase (sGC) Activator Runcaciguat Are Associated with Distinct Changes in Renal Gene Expression Profiles**

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**Background:** Chronic kidney disease (CKD) progression is associated with impaired NO-sGC-cGMP-signaling, low cGMP production and increased oxidative stress. Oxidative stress modifies the native sGC to oxidized, heme-free apo-sGC which cannot be activated by NO anymore. Runcaciguat is a novel potent and selective sGC activator that binds and activates heme-free sGC independently of NO and, thereby, restores cGMP signaling. In the ZSF-1 rat CKD-model, runcaciguat displays renoprotective effects (pronounced decrease in proteinuria and lowering of HbA1c and triglycerides). To understand the underlying mode of action of the renoprotective and metabolic effects of runcaciguat, we investigated the renal gene expression profile.

**Methods:** The renal expression profile of genes affected by 3mg/kg/bid runcaciguat in the ZSF-1 rat CKD-model was analyzed with a microarray analysis (IPA). The renal expression profile of genes affected by 3mg/kg/bid runcaciguat was analyzed with a microarray analysis (IPA).

**Results:** The renal expression profile of genes affected by 3mg/kg/bid runcaciguat was analyzed with a microarray analysis (IPA). The renal expression profile of genes affected by 3mg/kg/bid runcaciguat was analyzed with a microarray analysis (IPA).
Conclusions: The runcicagin-induced gene expression changes clearly indicate an at least partial reversal of the fibrotic phenotype and enhanced vascular-endothelial functions in the ZSF-1 CKD rat model. These changes could contribute to the renoprotective effect of runcicagin. Runcicagin is currently evaluated in a Ph2a clinical trial (CONCORD) for CKD.

Funding: Commercial Support - Bayer AG

PO0709
Exogenous Hydrogen Sulfide Protects Kidneys of Diabetic Mice from Oxidative Injuries
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Background: Exogenous hydrogen sulfide (H2S) protects kidneys from diabetic injuries in animal models. In order to explore its mechanisms, we determined the effects of H2S donor on renal reactive oxygen species (ROS) related enzymes in diabetic mice.

Methods: Male C57Bl/6j mice (8 weeks old) were intraperitoneally injected with STZ at 50mg/kg/day for 6 days. GYY4137 (20 mg/kg/day in 6 ml of drinking water, GYY+DM group, n=5) or vehicle (6 ml of drinking water, DM group, n=4) plus 60% fat diet were fed the mice 2 weeks after the initial STZ injection when blood glucose remained high relative to background mice. The 2 groups of diabetic mice were injected with long-acting insulin (10U/kg) weekly at week 3.

Results: GYY4137 ameliorated albuminuria and hyperglycemia at weeks 8 & 10. Serum insulin and creatinine were similar in the diabetic mice. Renal morphology structures (HE, Masson, PAS) were improved by GYY4137 at week 10 when the mice were sacrificed. Renal nitrotyrosine (protein oxidative injury marker) was decreased along with the decrease of laminin (early fibrosis marker) in GYY+DM mice relative to DM mice (western blotting). NOX2, NOX4 were lower but NOS1, HO2, PON1, PON2 were higher in GYY+DM than those in DM group. NOX2, NOX3, NOX1, HO1, SO2D3-1 and COX1 were similar between groups. The levels of mRNA were not in agreement with the changes in proteins with all enzymes but HO2.

Conclusions: Our findings suggest that exogenous H2S may decrease ROS production and increase ROS cleavage in kidney via the affected enzymes, thus improve the renal oxidative damage in diabetic nephropathy.

PO0710
Downregulation of Ethhahd and Tubular Dysfunction in Diabetic Nephropathy
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Background: As a peroxisomal protein, enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase (Ethhahd) catalyzes the second and third committed steps in the peroxisomal beta-oxidation pathway. Ethhahd also interacts with catalase and peroxisomal biogenesis factor 5 (PEX5), which decomposes hydrogen peroxide and regulates peroxisomal biogenesis, respectively. Previously we detected reduced tubular Ethhahd expression in human and mouse diabetic nephropathy. This study aims to investigate the potential impact of Ethhahd on peroxisomal/mitochondria functional change in response to high glucose in vitro.

Methods: Primary cultured proximal tubular epithelial cells (PTC) were exposed to high glucose, mannitol or control medium. Ethhahd subcellular localization and peroxisome quantitation (area per cell) were analyzed by confocal microscopy. Ethhahd, catalase, PEX5, ACOX1, Hsd17d4, scp2, ACAA1, cpt1a, Acadm, AHDBB, Acat1 and ACAA2 mRNA expression were assessed by qPCR. Peroxidase activity and oxidative stress were also analyzed.

Results: Ethhahd transcription and protein were significantly downregulated in PTC under high glucose conditions. Ethhahd was localized mostly to peroxisomes and rarely in mitochondria. Key enzymes for beta-oxidation in peroxisomes (ACOX1, Hsd17d4, scp2 and ACAA1) and mitochondria (cpt1a, Acadm, AHDBB, Acat1 and ACAA2) were not changed under high glucose conditions. Catalase transcription and peroxisome activity were reduced in high glucose vs control. PEX5 was also reduced, but peroxisome quantitation was increased 39.6% under high glucose conditions. Oxidative stress was also increased 7.6% in high glucose vs control.

Conclusions: Ethhahd downregulation is associated with reduced peroxidase activity, increased peroxisomal biogenesis and oxidative stress in PTC. Whether altering Ethhahd can impact such dysfunction awaits further study.

Funding: NIDDK Support

PO0711
Oxidative Stress on the Kidney and Heart of Rats with Diabetic Nephropathy Treated with Esculin
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Background: Diabetes mellitus is a chronic disease which progresses with complications such as diabetic nephropathy (DN) and diabetic cardiomyopathy. Esculin (ESC) and its metabolite, esculentin, are coumarin derivatives, belonging to the Oleaceae family, found also in some more known species in the southern hemisphere, such as the pink lemon (Citrus limonia). ESC has been related to antioxidant (AO), anti-inflammatory and anti-apoptotic actions. The aim of the present study was to verify the role of oxidative stress (OS) on the kidney and the heart of rats with DN, and the ESC effect on them.

Methods: We used adult male Wistar rats (N=20), Ethics Committee # 3511260318. Normal rats (CTR) or with blood glucose > 200mg/dL (diabetic (DM), treated with streptozotocin 60 mg/kg, IV, single dose), received ESC (50 mg/kg, i.p. control, 4mg/kg, for 8 weeks). After this period, we collected blood, 24-hr urine, the kidney and heart of these animals. The organs were homogenized for TBARS (OS marker) and Western blotting of OS and apoptosis markers.

Results: Renal function assessed by urea and creatinine was reduced in DM x CTR. Proteinuria and TBARS increased in plasma and urine in DM rats, with a reduction in DM x ESC group (p<0.05). In DM heart, there were no alterations in TBARS; glutathione, a pro-oxidant, was elevated. In the heart, Nrf-2, responsible for the transcription of several AO, was elevated in the DM, both in its cytoplasmic form and in its active, phosphorylated form. Catalase, an enzymatic AO, and caspase-3 were elevated in DM (p<0.05).

Conclusions: ESC protected the diabetic kidneys reducing proteinuria and OS. Unlike the kidney, the hearts of DM did not present OS, although glutathione and apoptosis were increased in ESC treated group. The ESC may provide an antioxidative effect on the heart of diabetic rats. These findings may be useful in the approach of prevention and treatment of cardiomypathy, including the possible use of esculin, with its important antioxidant, anti-inflammatory and anti-apoptotic effects, as an adjuvant therapy.

Funding: Government Support - Non-U.S.

PO0712
Targeting Nox with Pan-Nox Inhibitor in Aging Diabetic Kidney
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Background: Aging process is a risk factor for altered glucose metabolism and insulin resistance. Moreover, diabetes with serious complications has been steadily increasing in older patients. Chronic inflammation and increased oxidative stress are commonly shared features of aging and diabetes mellitus. Therefore, we investigated the effect of pan-nox inhibitor on aging diabetic mice.

Methods: Diabetes was induced by intraperitoneal injection of streptozotocin at a 50mg/kg/day for 5 days in 52-week-old C57BL/6j mice. An orally active pan-nox inhibitor from Aptebo was administered by oral gavage at a dose of 60mg/kg/day for 12 weeks in aging mice and diabetes induced aging mice.

Results: Nox inhibition significantly improved insulin resistance in both aging and diabetic aging mice. Interestingly, oxidative stress measured by 8-isoprostane was significantly increased in both aging and diabetic mice. Pan-nox inhibitor significantly reduced plasma 8-isoprostane level in aging group, and urinary 8-isoprostane level in diabetic group. In diabetic aging condition, there was trend to decrease in urinary albumin and nephrin excretion with nox inhibition. Simply aging did not significantly altered PAI-1 and collagen IV expressions in the kidney compared to diabetic condition. However, nox 1 and 4 expressions was as well as increased in aging mice and it is important to note, however, that the increase of NOX proteins such as Nrf2 and catalase, suggests that at this early stage of DN, they are still able to protect the cardiac tissue against OS. We believe that the monitoring of this disease evolution can better clarify the role of Redox balance/imbalance in the heart of diabetic rats. This would be very useful in the approach of prevention and treatment of cardiomypathy, including the possible use of esculin, with its important antioxidant, anti-inflammatory and anti-apoptotic effects, as an adjuvant therapy.

Funding: Government Support - Non-U.S.
NOX5 Promotes Diabetic Kidney Disease by Modulating Redox-Sensitive Pathways
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Background: Enhanced level of reactive oxygen species (ROS) in diabetes is considered a major contributor in aggravating renal injury. We aimed to examine the role of pro-oxidant enzyme NOX5 and associated redox-sensitive pathways in diabetic kidney disease (DKD).

Methods: We examined the expression of NOX5 and associated redox-sensitive factors including NOX4, thioredoxin-interacting protein (TXNIP), a transcription factor, EGR1 (early growth response 1) and a protein kinase, PKC-α as well as ROS production in human kidney biopsies and in human renal cell lines as well as in human kidney organoids. We also assessed the effect of NOX5 expression independent of NOX4 in Nox5 transgenic mice in the presence or absence of diabetes.

Results: We observed increased expression of NOX5 in diabetic patients in association with upregulation of ROS-sensitive factors including EGR-1, PKC-α and TXNIP. We also observed upregulation of human NOX5 and TXNIP in renal organs exposed to high glucose. Silencing of Nox5 attenuated high glucose induced gene expression of markers of fibrosis and inflammation as well as downregulation of EGR-1, PKC-α and TXNIP. Our data also suggest that Nox5 is upstream of Nox4 and that Nox5 inhibition also downregulates Nox4, but not vice versa. In vivo, overexpression of Nox5 independent of NOX4 pathways demonstrated an increase in albuminuria, renal fibrosis and inflammation in association with upregulation of EGR-1, PKC-α, TXNIP and enhanced ROS production in comparison to diabetic mice not expressing Nox5.

Conclusions: These findings suggest that NOX5 plays a key pathogenic role in renal inflammation and fibrosis, thereby providing impetus for the development of NOX5 specific inhibitor to combat DKD.

PO0714 Hyperpolarized MRI Detection of Dapagliflozin Effect on Gluconeogenesis in Live Animals: Proof of Principle
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Background: SGLT2 inhibitors including dapagliflozin (dapa) ameliorate hyperglycemia by inducing glucosuria but also induce gluconeogenesis (GNG), thus blunting efficacy. The lack of insight into the relative contributions of kidney and liver to GNG in different states is due in large part to limitations in the technology to separately assess liver and kidney GNG in live animals. Our study exploits a powerful technology, Hyperpolarized Magnetic Resonance Imaging (HP-MRI), which can detect metabolic substrates via dissolution dynamic nuclear polarization (DNP). To account for potential limitations in cancers.

Methods: Metabolic features of healthy WT (male, age ~12 weeks) rats were studied in vivo using hyperpolarized (HP) 13C magnetic resonance imaging (MRI) is based on ~50,000-fold nuclear magnetic resonance (NMR) signal enhancements of 13C-labeled substrates via dissolution dynamic nuclear polarization (DNP). To account for potential metabolic effects of insulin, we also performed [1-13C]pyruvate tolerance tests (PTT).

Results: We successfully detected the conversion of [1-13C]pyruvate to [1-13C]lactate and [1-13C]alanine in the liver and kidneys of rats. We found that Intravenously injected [1-13C]pyruvate was rapidly metabolized to [1-13C]lactate and [1-13C]alanine in the liver and kidneys of rats. The PTT data show that there is a clear trend toward an increase in blood glucose following [1-13C]pyruvate injection. Dapa increased glycosuria, as expected. Furthermore, an effect of dapa was on the conversion of [1-13C]pyruvate to [1-13C]lactate and [1-13C]alanine in the kidney but not the liver. This effect, however, was variable and appeared to be influenced by baseline GNG in the rats.

Conclusions: We establish here for the first time that HP-MRI technology can detect SGLT2 effects on metabolism in live rats, and can distinguish metabolic markers in cancers.

PO0715 Investigation of the Renoprotective Effect of SGLT2 Inhibitors Focused on Glucomeral Hyperfiltration and Oxidative Stress in Mice with Diabetic Kidney Disease
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Background: In recent clinical trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors slowed the progression of DKD compared with placebo. One of the main mechanisms for the renoprotective effect of SGLT2 inhibitors in DKD is the improvement of hemodynamics. However, we previously demonstrated that the underdosing of SGLT2 inhibitors may lead to an A1 receptor pathway played a pivotal role in the tubulo-glomerular feedback system in type 1 diabetic model mice (Circulation, 2019). We also reported that increased glomerular oxidative stress was involved in the progression of albuminuria in DKD (Diabetologia, 2010). Loss of trihydroxybipterin (B8H4), which is a cofactor of eNOS, causes uncoupling of endothelial nitric oxide (NO) synthase (eNOS), resulting in increased superoxide production in DKD (JAPPRP, 2005; JASN, 2013). In this study, we explored the renal protective effects of SGLT2 inhibition, with a focus on glomerular hemodynamics and glomerular oxidative stress.

Methods: We used db/db mice as a model for type 2 diabetes. Mice were treated with canagliflozin (CANA; 10mg/kg) for 8 weeks. We evaluated the change of single nephron glomerular filtration rate (SNGFR) and glomerular permeability of albumin using in vivo multiphoton microscopy imaging. Glomerular reactive oxygen species (ROS) and NO production were evaluated by ex vivo study. Low temperature-sulfate-polyacrylamide gel electrophoresis was performed for detection of eNOS uncoupling. In addition, tomato lectin staining was carried out to estimate the vascular endothelial damage.

Results: Glomerular hypertension and urinary albumin excretion in db/db mice was ameliorated by CANA treatment. Accelerated ROs production and diminished bioavailable NO caused by eNOS uncoupling in glomeruli were observed in db/db mice. CANA suppressed eNOS uncoupling and improved ROS/NO imbalance via maintenance of vascular endothelial damage.

Conclusions: SGLT2 inhibitor restore glomerular hypertension in DKD. Intriguingly, intraglomerular ROS/NO imbalance via eNOS uncoupling was improved by SGLT2 inhibitor.
albumin creatinine ratio (uACR), KIM-1, NGAL and cleaved caspase 3 expression in the renal cortex of mice in an early phase of DKD. Kim1 and NGAL upregulation was examined by qPCR of genes related to glycolysis, TCA cycle and fatty acid oxidation.

**Results:** Similar degree of HFD-induced obesity occurred in both SGLT2 mutant and WT mice while compensatory hyperphagia was observed only in mutant mice. HFD led to elevation of post-prandial blood glucose level, glucose intolerance and insulin resistance. Increases in postprandial blood glucose and glucose intolerance were blunted in SGLT2 mutant mice. Although changes of GFR and urinary albumin excretion were not observed, Kim1 and NGAL expression were upregulated by HFD feeding, indicating that mice developed pathological changes in an early phase of DKD. Kim1 and NGAL upregulation was abrogated in SGLT2 mutant mice. Furthermore, HFD feeding induced apoptosis in the cortex of WT mice, but not in SGLT2 mutants. Kidney/body weight ratio was decreased by HFD in WT but increased in SGLT2 mutant mice, suggesting metabolic differences in the kidney. Genes related to glycolysis (PGK and PKM), TCA cycle (IDH2) and fatty acid oxidation (CPT1a, CPT2, PPARα and PGC1α) were suppressed in SGLT2 mutant vs WT HFD groups.

**Conclusions:** SGLT2 inhibition ameliorates tubular injury associated with renal hypertrophy and metabolic suppression in very early phase of diet-induced DKD.

**Funding:** NIDDK Support

**PO0718**

**mTORC2 Is Essential for Sodium-Glucose Cotransporter 2**

Wahed Shabab, John E. Demko, Enzo Takagi, Bidusha Saha, Deise C. Leite-Dellova, Bharathi Dellova, Mahendra Soler.1

**Background:** The role of mammalian target of rapamycin (mTOR) complexes mTORC1 and mTORC2 in renal tubule ion transport has been well characterized. We and others have shown that mTORC2 is a key regulatory kinase for serum and glucocorticoid kinase 1 (SGK1) and that its activity is required for epithelial Na⁺ channel (ENaC)-dependent sodium reabsorption in the aldosterone-sensitive distal nephron (ASDN). Also, we showed that mTORC2 activation is required in proximal tubule cells (RPTCs) in diabetes, which was prevented by the inhibition of sodium-glucose co-transporter 2 (SGLT2), and that mTORC1 KO in mice causes a Fanconi’s syndrome-like phenotype. However, the roles of mTORC2 in the regulation of RPTC transporters, particularly as it pertains to glucose reabsorption remain obscure. In this study we explored the relationship between mTORC2 and SGLT2 in CRISPR-modified HEK-293Tells and in mice, using patch clamp and membrane expression studies.

**Methods:** We used CRISPR-Cas9 to generate Sin1 (an essential component of mTORC2) knockout HEK-293T cells, which were compared with wild-type cells. The cells were transiently transfected with SGLT2L. We recorded in WT HEK-293T cells the Dapa-sensitive SGLT2 sodium current. We used an inducible Cre-lox system (Pax8-Lox) to KO Rictor (another key component of mTORC2) in mice. Dapagliflozin-sensitive whole-cell SGLT2 sodium current was measured in the microdissected proximal tubules and HEK-293T cells.

**Results:** Strikingly, in mTORC2-knockout HEK-293T cells the Dapa-sensitive SGLT2 sodium current was significantly reduced versus WT HEK-293T cells. In mice, mTORC2 KO caused glycocaemia without hyperglycaemia, and patch-clamp studies showed decreased glucose-induced, dapagliflozin-inhibited Na⁺ current.

**Conclusions:** Knockout of mTORC2 in the HEK-293T cells or in mice inhibits SGLT2-sodium current. Our study delineates the essential role of mTORC2 in SGLT2 function in vivo. These observations explain the broad role of SGLT2 inhibition therapy and variable resistance to their effects.

**Funding:** NIDDK Support

**PO0719**

**MAP17 and D-AKAP-2, Two Major Scaffolding Proteins, Are Upregulated in Experimental Diabetic Nephropathy in Response to Empagliflozin on Top of RAS Blockade**

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**Background:** Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have proven to delay diabetic nephropathy (DN) progression on top of the standard of care renin-angiotensin system (RAS) blockade. This protection was mostly attributed to improvement in renal hemodynamics although direct effects on the kidney cannot be ruled out. Further, the molecular mechanisms underlying the synergic effect of SGLT2i and RAS blockers is unknown.

**Methods:** 12 weeks old diabetic db/db mice were given empagliflozin (10mg/Kg/day), ramipril (8 mg/Kg/day) or the combination of both drugs during 8 weeks. Mice treated db/db and db/m mice were used as controls. Serum glucose, blood pressure, GFR and albuminuria were measured at baseline and at the end of study. At the end of the experiment, mice were euthanized and the kidneys were saved for a differential high-throughput proteomic analysis by mass spectrometry using isobaric tandem mass tags (TMT labelling).

**Results:** Vehicle db/db mice showed increased glycemia during the whole experiment and empagliflozin normalized blood glucose. Ramipril treatment decreased blood pressure. Diabetic vehicle mice showed inceptent DN, mesangial expansion and albuminuria were significantly increased when compared to their non-diabetic littersmates. All the treatments reduced mesangial expansion and albuminuria. The differential expression analysis revealed differences in one of the experimental groups (FDR < 0.05 and Log FC>1); among them MAP17 and D-AKAP-2 were upregulated in the kidney of the db/db treated with empagliflozin with ramipril. We validated these findings by western blot.

**Conclusions:** The combined therapy of empagliflozin with ramipril upregulated both MAP17 and D-AKAP-2 in the kidney of a diabetic mice model. MAP17 and D-AKAP-2 are two major scaffolding proteins found in the proximal tubular cells that place transporters together such as SGLT2 and NHE3 and also regulate the function of protein kinases like SGK1 which in turns inactivates NHE3 by phosphorylation. Our results suggest that SGLT2i on top of RAS blockade may protect the kidney by boosting the inactivation of NHE3 via the upregulation of key scaffold proteins such as MAP17 and D-AKAP-2.

**Funding:** Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.
Methods: Obese diabetic and hypertensive ZSF1 rats were treated with vehicle, enalapril (10 mg/kg, p.o.), or empagliflozin (30 mg/kg, p.o.) for 8 weeks. Along with phenotypic parameters, Olink Mouse Explorative panel was used to simultaneously detect the levels of 92 proteins in plasma and urine samples using the proximity extension assay.

Results: Compared to vehicle and enalapril, empagliflozin reduced blood glucose, HbA1c, and urinary albumin levels while increasing HDL levels in ZSF1 rats. Empagliflozin significantly affected the levels of 16 proteins in plasma samples. Lower plasma concentrations after empagliflozin-treatment were detected for Notch3, tenasin-R, glial cell line-derived neurotrophic factor, and erythropoietin. In urine, we found significantly increased levels of αSMA, TIMP-1, E-cadherin, and VEGF-A (p<0.001). There were no significant changes in the concentration of TGF-β, the main predictor of renal function in diabetic kidney disease, in plasma and urine samples.

Conclusions: Reduced levels of Notch3, tenasin-R, and erythropoietin and increased levels of TIMP-1, E-cadherin, and VEGF-A indicate the potential of empagliflozin to improve renal function in diabetic kidney disease.

Methods: Under fixed sodium intake (2 mmol NaCl/kg body weight/day) for 4 days before and after GLP-1 treatment, 10 lean healthy male participants were examined twice in random order during a 1-hour infusion of either GLP-1 (1.5 pmol/kg/min) or vehicle (0.9% NaCl) together with an intravenous infusion of 0.9% NaCl (750 mL/h). Interleaved measurements of renal artery flow, oxygenation (R2*), and perfusion (arterial spin labeling) were acquired in the renal cortex and medulla, using Magnetic Resonance Imaging (MRI) during infusions.

Results: During GLP-1 infusion, medullary perfusion increased 32 ± 7% (p<0.001) and cortical perfusion increased 13 ± 4% (p<0.001) compared to vehicle where medullary and cortical perfusion decreased (p<0.001). A1aR antagonist abolished increased R2* values increased 3 ± 2% (p=0.025) in the medulla and 4 ± 1% (p=0.008) in the cortex during vehicle infusion (indicative of decreased oxygenation) but remained unchanged during GLP-1 infusion. Renal arterial blood flow was not altered significantly by either intervention.

Conclusions: GLP-1 increases mainly medullary but also renal cortical perfusion and oxygenation during NaCl loading. In perspective, GLP-1 may promote Na excretion through this mechanism and exert long-term protective effects against hyperfiltration and ischemic injury.

PO0722
Elucidation of Glomerular Hemodynamic Changes by SGLT2 Inhibitors and ARBs in a Type 2 Diabetic Animal Model Using In Vivo Imaging

Methods: In recent clinical trials have shown that SGLT2 inhibitors (SGLT2i) inhibit the progression of diabetic kidney disease (DKD). We established the method for measuring single-nephron GFR (SNGFR) in mice by in vivo imaging and found that the adenine / adenine A1 receptor (A1AR) pathway in tubuloglomerular feedback (TGF) is involved in the pathogenesis of glomerular hyperfiltration (GH) in DKD using type 1 diabetic animal model (Kidokoro K. et al. Circulation 2019). The mechanism of development of GH, and improvement of GH by SGLT2i is considered to be different in type 2 diabetes. However, the detailed regulatory mechanism of GH in TGF has not been elucidated in type 2 DKD. We conducted experiments to elucidate the glomerular hemodynamic changes in type 2 diabetic animal model, using SGLT2i alone and in combination with RAAS inhibitors.

Results: SGLT2i + ARB combination group and measured AA, EA, and glomerular volume. SGLT2i showed significant increase in blood glucose and urinary protein levels compared to ZL. SNGFR, AA, EA and SNGFR were observed every 30 minutes after SGLT2i administration. Furthermore, we investigated the involvement of the adenine / A1AR pathway in type 2 diabetic animals using an A1AR antagonist (A1aRant). We made a SGLT2i + ARB combination group and measured AA, EA, and glomerular volume.

Conclusions: Our results showed that the regulation of AA vascular smooth muscle with an adenine / A1AR antagonist (A1aRant) was involved in the GH in type 2 DKD.

PO0724
Cirrhosis Is Upreregulated in Type 2 Diabetes, Impairing Insulin Signaling in Skeletal Muscles and Adipose Tissues

Methods: We hypothesized that alkali or acid loading would promote varying levels of AA. α-SMA, and oxygenation during NaCl loading. We identified biomarkers that are associated with SGLT2i and ACEi treatment. Our results may additionally provide mechanistic insights into the beneficial effects of SGLT2i and ACEi treatment in ZDF. Glomerular volume was significantly increased, while there were no significant changes about blood pressure, but urinary protein excretion was significantly suppressed by ARB treatment in ZDF. Glomerular volume was significantly increased, while there were no significant changes in AA and EA. SGLT2i ameliorated abnormal expansion of AA also in the presence of ARB, and no change in EA.

Results: Control mice with HFD displayed impaired insulin signaling with reduced tyrosine phosphorylation of the IGF1R, PI3 kinases and pAkt (ser473) in skeletal muscles. However, in SIRPα KO mice with HFD there was no downregulation of these insulin signaling proteins. Next, we examined adipose tissues of these mice and found impaired pAkt in control mice fed a HFD. In SIRPα KO mice pAkt signaling remained intact despite exposure to HFD. Next, control mice exposed to HFD displayed increased activation of pAkt, TT, and treatment of myotubes with recombinant SIRPα were performed.

Conclusions: Suppression of SIRPα in a HFD model of type 2 diabetes improves insulin resistance and is a potential therapeutic target for the treatment of type 2 diabetes.

Funding: Other NIH Support - NHLBI

PO0725
Metabolic Acidosis Does Not Impair Insulin Sensitivity in Rats with CKD

Methods: Metabolic acidosis is a major etiology of chronic kidney disease (CKD) is diabetes mellitus. Even at early stages of CKD with near normal GFR, impaired insulin signaling is present, suggesting an early trigger of insulin resistance. We have discovered a potential driver of insulin resistance, signal regulatory protein alpha (SIRPα) which adversely influences skeletal muscles and adipose tissues in a model of type 2 diabetes.

Results: Control mice with global SIRPα knockout (KO) mice were subjected to HFD for 12 weeks. Glucose (GTT) and insulin tolerance tests (ITT), immunoblots, and treatment of myotubes with recombinant SIRPα were performed. n=6 mice/group, results are presented as mean ± SD.

Conclusions: Suppression of SIRPα in a HFD model of type 2 diabetes improves insulin resistance and is a potential therapeutic target for the treatment of type 2 diabetes.
2/3 nephrectomy (n=7; Nx) or 5/6 Nx (n=4). Rats recovered for 4 weeks, then underwent insulin tolerance testing (ITT; 0.75 U/kg i.v.) before and after alkali (2 weeks 0.1M NaHCO₃) and acid loading (1 week 0.1M NH₄Cl) in the drinking water. Male Zucker obese rats (10 wks) underwent 5/6 Nx (n=4) and were also given 4 weeks of recovery before being placed on 0.1M NH₄Cl for 4 days.

Results: In Nx SD rats, 0.1M NaHCO₃ did not produce metabolic alkalosis (Table 1) or reduce insulin sensitivity (Plevel of Nx=0.67). 0.1M NH₄Cl in Nx SD rats produced a mild metabolic acidosis (Table 1). However, this did not alter the response to insulin (Plevel ofNx=0.56). 0.1M NH₄Cl produced a severe metabolic acidosis in Zucker rats with 5/6-Nx (Table 1). Again, however, this was not associated with an impaired insulin response. Rather, following NH₄Cl loading, Zucker rats had a greater response to insulin (Plevel of Nx=0.01). Unexpectedly, we observed a negative relationship between the magnitude of change in blood glucose (inverse area under the curve) and plasma pH (r=-0.27, P=0.003) and plasma HCO₃^- (r=-0.33, P=0.009) in renalized kidney rats.

Conclusions: These data demonstrate that metabolic acidosis does not impair insulin sensitivity in rats. Our data suggest that the direct effects of metabolic acidosis are unlikely to underlie significant impairments in insulin sensitivity in CKD. Funding: Other NIH Support - P01HL134664 (to PMO), R21AI150723 (to PMO)

Table 1.

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PO0726 Understanding Mechanisms Underlying Diabetic Kidney Disease Using Integrative Transcriptome and Proteome Profiling of Insulin-Resistant Human Cell Lines

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Background: One of the strongest metabolic features of diabetic kidney disease (DDK), in both type 1 and type 2 diabetes, is insulin resistance and it is increasingly clear that disruptions to renal cellular insulin responses can drive DDK development. The present study aims to generate a comprehensive network of molecular changes occurring in the kidney in response to insulin resistance using cell models.

Methods: Conditionally immortalised human podocytes (Pod), glomerular endothelial cells (GEC), mesangial cells (MC) and proximal tubular cells (PTC) were studied. A diabetic, insulin resistant, environment was established using a combination of TNFα, IL-6, high glucose and high insulin. The cellular proteome and transcriptome were studied simultaneously using Tandem-Mass-tagged mass spectrometry and RNA sequencing. To explore the changes occurring in insulin resistance, integrated transcriptome and proteome data were analysed using univariate and multivariate statistical models and gene set enrichment analysis (GSEA) was performed to identify significantly regulated cellular processes.

Results: Initial results revealed that exposure to a diabetic environment induced differential insulin resistance between human kidney cell lines. Differential expression analysis of both transcriptome and proteome found that insulin resistance had the most differential insulin resistance between human kidney cell lines. Differential expression statistical models and gene set enrichment analysis (GSEA) was performed to identify these genes/proteins. GSEA identified consistent increases in the inflammatory response, ER stress and cell proliferation. These data demonstrate that metabolic acidosis does not impair insulin sensitivity in rats. Our data suggest that the direct effects of metabolic acidosis are unlikely to underlie significant impairments in insulin sensitivity in CKD. Funding: Other NIH Support - P01HL134664 (to PMO), R21AI150723 (to PMO)

PO0727 Insulin Resistance Is Associated with Decreased Renal Insulin Receptor Beta in Aged D4 Null Mice

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Background: Insulin resistance is a major concern in metabolic disorders related to diabetes.

Methods: In order to explore the hypothesis that D4 dopamine receptor (D4R) increases insulin sensitivity through its activation of insulin receptor beta (IR-beta), we demonstrated the functional role of D4R in the prevention of insulin resistance by studying D4R null (Drd4^-/-) mice and wild-type (Drd4^+/-) littermates.

Results: We found that Drd4^-/- mice (14 mos) had increased fasting blood glucose regardless of sex but their urines were negative for glucose and ketones, suggesting that the mice fed normal salt/normal fat diet were pre-diabetic. Serum insulin levels were increased in male Drd4^-/- mice but not altered in female Drd4^-/- mice after an 8 hr fast indicating that these mice have resistance or insensitivity to endogenous insulin. The aged male and female Drd4^-/- mice had similar body weights, fasting serum total and free cholesterol, triglycerides, to their age and sex-matched Drd4^+/- littermates, suggesting that the old Drd4^-/- mice were not obese and had no dyslipidemia. Relative to Drd4^+/- littermates (100±7%, n=6), Drd4^-/- mice had decreased IR-beta (194±4%, n=4) but normal peripheral gene expressions of IR-alpha, insulin degrading enzyme, insulin substrate 1, sodium glucose transporter 2 and glucose transporters in renal cortex homogenates, indicating that the decreased protein expression of IR-beta contributed to the insulin resistance in the aged Drd4^-/- mice. Drd4^-/- mice had decreased phosphorylated IR-beta at Tyr1631&1634, and Tyr1142. Renal expression of insulin receptor beta was located in mouse renal glomeruli and tubules and co-localized the apical membrane with NCC in the distal convoluted tubules in cortex and NKCC2 in the thick ascending limbs of loop of Henle in the outer medulla. D4R and IR-beta were co-immunoprecipitated in immortalized mouse renal distal convoluted tubule cells and the co-immunoprecipitation was increased by D4R agonist and not altered by D4R antagonist. The Core Laboratory, Nanjing BenQ Medical center, The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, China; 2Medical University of South Carolina, Charleston, SC.

Acknowledgment: These data indicate that renal mass reduction increases the response to exogenous insulin independent of the level of underlying insulin resistance, and that this is not mediated by an increased half-life of circulating insulin. Further investigation into the factors that contribute to increased insulin responses in CKD may identify novel targets for the treatment of insulin resistance.

Funding: Other NIH Support - P01HL134664 (to PMO), R21AI150723 (to PMO)

Figure 1.

PO0729 The Essential Role of Intact Mitochondrial Substrate Balance in Preventing Renal Injury

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Background: Alterations in mitochondrial function are linked to the development of chronic/diabetic kidney diseases. Proximal tubular cells (PTCs) are highly energy demanding, covering this requirement mostly from mitochondrial fatty acid oxidation, and it is suggested, but not entirely clear whether derailments in mitochondrial metabolism and function are forerunners of tubular damage. In our previous studies we modeled mitochondrial substrate overload - an important aspect of metabolic disease - by creating renalized cells and functionally disrupting the enzyme carnitine palmitoyltransferase 1. These studies revealed that mitochondrial substrate overload in proximal tubules causes tubular injury and secondary glomerulosclerosis.

Funding: Other NIH Support - P01HL134664 (to PMO), R21AI150723 (to PMO)
Methods: Here we demonstrate the importance of intact mitochondrial substrate efflux in protecting the kidney against the deleterious effects of overload of the generated circuit of a homeostatic CrAT knockout mouse model ("PT-CrAT" mouse). We used an integrated approach of imaging, electron microscopy, functional studies (mitochondrial/cell respiration) and Next Generation RNA Sequencing combined with Ingenuity Pathway Analysis.

Results: PT-CrAT mice developed tubular and glomerular injury similarly to their homozygous counterparts (N=5-7 mice examined, at least three separate cohorts). Mitochondria were structurally and functionally impaired in both sexes. Transcriptomic analyses, however, revealed striking differences in the pathways leading to renal injury in males, with a strong focusing on Neftofibrosis (with a threshold of P<0.1). In response to CrAT haploinsufficiency, males almost completely shut down fatty acid oxidation and related pathways. Females had a much weaker transcriptional response in metabolism-related pathways but activation of inflammation was more prominent when compared to males. Proximal tubular cells from these animals exhibited a shift in metabolism towards a more glycolytic phenotype (N=8 biological replicates, P<0.05 in at least three independent experiments), which was also more pronounced in males.

Conclusions: Our findings demonstrate that maintaining an intact mitochondrial substrate metabolism balance is crucial for the PTC. Potentially broad implications are: the metabolic shift and the sexual dimorphisms discovered herein offer new intervention points for the future and novel approaches to consider for treating kidney disease.

Funding: NIDDK Support

PO0730

Spexin-Based Galanin Receptor 2 Agonist (NS200) Improves Diabetic Nephropathy in Type 2 Diabetes


Background: Spexin is a novel neuropeptide having an emerging role in metabolic diseases such as obesity and diabetes and involved in energy homeostasis and food intake regulation. The spexin-like-examined galanin receptor 2 agonist (NS200) has anti-diabetic activity and anxiolytic effect. The aim of this study is to investigate the effect of NS200 on insulin resistance and diabetic nephropathy in type 2 diabetic animal.

Methods: 8 to 10 week old db/db and db/db mice were treated with NS200 for 12 weeks. NS200 was administered by intraperitoneal injection at a dose of 1.0 mg/kg/day as reported in the previous study.

Results: There were no changes in body weight, food and water intake, urine volume, fasting glucose level and HbA1c level by NS200 treatment in diabetic mice. Insulin tolerance test and glucose tolerance test were also unchanged by treatment. NS200 lowered systolic blood pressure. Interestingly, NS200 improved urinary albumin excretion significantly in diabetic mice. Renal histology showed reduced glomerulosclerosis and tubulointerstitial fibrosis in treatment groups. Renal TGFβ and type IV collagen expressions were decreased in NS200 treated group, whereas PAI-1 showed no change. NS200 treatment in diabetic mice showed renoprotective effects in urinary albumin excretion and renal structural changes.

Conclusions: Our results provide the evidence that spexin-based galanin receptor 2 agonist by NS200 has renoprotective effect in diabetic nephropathy. These findings suggest a mechanism via its inhibition of renal insulin signaling pathway therefore provide a considerable promise as a new agent in diabetic nephropathy.

PO0731

Cell Sex and Sex Hormones Regulate Kidney Metabolism of Glucose and Glutamine: Implications for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the major cause of end-stage kidney disease. Male sex is a risk factor for DKD, but the reasons for this predilection are unclear. We demonstrated that androgens accentuate DKD in vivo, and that sex differences in uncoupled glucose and glutamine metabolism, in male proximal tubular epithelial cells (PTECs). We aimed to determine the effect of cell sex and sex hormones on kidney metabolism.

Methods: Male and female PTECs were stimulated with control, dihydrotestosterone (DHT), or estradiol. Sex differences in key metabolites were validated in diabetic mice, and in type 2 diabetic patients and their age- and weight-matched healthy controls (n=180, iCARE cohort).

Results: Male PTECs showed significantly higher glycolysis, oxygen consumption (OCR), glucose consumption, oxidative stress, and apoptosis, compared to female PTECs, especially in the presence of DHT. Higher OCR in male PTECs was further enhanced in the presence of glucose and glutamine, but not observed in the presence of pyruvate. A male sex hormonal bias (DHT) in PTECs showed a decline in OCR and ATP levels over time, and increased lactate production. Male PTECs had significantly higher intracellular levels of TCA cycle metabolites (glutamate, citrate, malate, aspartate) and glutathione metabolites. In turn, female cells had higher levels of pyruvate. In vivo, male sex was highly associated with circulating levels of glucose, lactate, and glutamine in healthy and diabetic mice. Male sex was also independently associated with increased serum levels of glucose, succinate, fumarate, and 9 metabolites of the glutathione cycle, in healthy and diabetic individuals.

Conclusions: This is the first study to demonstrate that the kidney metabolism of glucose and glutamine is modulated by cell sex and sex hormones. Male sex was linked to increased oxidative stress, cell injury, glucose- and glutamine-related enzymes, lactate secretion, and levels of TCA cycle and glutathione metabolites. Our key findings will uncover physiological sex differences that are important for DKD and may lead to new therapeutic paradigms based on patient sex.

Funding: NIDDK Support

PO0732

Cirulating Fibroblast Growth Factor 20 (FGF-20) as a Novel Protein Protective Against Progression to ESKD in Diabetes

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Background: Growing evidence from animal, cellular and targeted biomarker studies supports an involvement of fibroblast growth factor (FGF) family members (FGF23, FGF21) in diabetic kidney disease (DKD) progression. However, the majority of the studies were cross-sectional and performed in a targeted manner focusing on individual proteins. Therefore, we aimed to comprehensively evaluate the profiles of circulating FGF proteins in progressive DKD leading to end-stage kidney disease (ESKD) in individuals with diabetes.

Methods: This was a prospective cohort study of individuals with type 1 (n=214) and type 2 (n=144) diabetes, persistent proteinuria and CKD Stage 3 followed for progression to ESKD within 10 years. Measurement of circulating FGF proteins (n=17) were performed in baseline plasma samples using aptamer-based (SOMAscan) proteomic profiling.

Results: One hundred eight (50%) and 35 (24%) individuals with T1D and T2D, respectively, developed ESKD within 10 years. Six out of 17 FGF proteins were protective against progression to ESKD in the univariable Cox regression model. The strongest protection was observed for FGF20 (HR (95% CI): 0.68 (0.59, 0.79), p=7.0x10^-8). The cumulative 10-year risk of ESKD was about 2 times lower in individuals with high versus low levels of FGF20. Three proteins remained significant after further adjustment by clinical covariates, however, only the protective effect of FGF20 was confirmed in a model of T1D individuals (n=214) and early ESKD (CKD Stage 1 and 2), (OR (95% CI): 0.48 (0.37, 0.61), p=6.1x10^-4). Interestingly, non-diabetic parents of T1D children with ESKD or Proteinuria had lower FGF20 concentrations than those parents with T1D children without kidney complications.

Conclusions: This study identified circulating FGF20 as protective against progression to ESKD in three independent cohorts of individuals with T1D and T2D and varying stages of DKD. The protective effect was independent from the clinical legacy measures of DKD. Identification of proteins that protect individuals from ESKD may be useful for the development of therapeutics for preventing or delaying the onset of ESKD.

Funding: NIDDK Support

PO0733

Proteome Analysis of Glomerular Formalin-Fixed Paraffin Embedded Kidney Samples Distinguishes Diabetic Nephropathy from Controls

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Background: Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is a sensitive technique for in depth proteome analysis but its usage as a diagnostic tool for kidney diseases is still in development. We investigated the potential use of LC-MS/MS in diagnosing diabetic nephropathy (DN) in renal biopsies.

Methods: Biopsies from 10 DN patients without renal comorbidity were compared to 10 pretreatment biopsies. Glomerular cross-sections were collected using laser capture microdissection and tryptic peptides were analyzed using LC-MS/MS. Resulting spectra were used for protein identification and further analysis.

Results: Based on all identified proteins, DN patients and controls clustered separately (Figure 1). Moreover, we identified 47 significant differentially expressed proteins for multiple testing. In DN proteins with increased expression included collagens IV, VI and XVIII, fibronectin, vitronectin, fibulin, complement component C3, C4 and C9, complement factor H, clusterin, fibronerin and apolipoprotein E. Proteins with decreased expression in DN included nephrin, chloride intracellular channel protein 5, Rab GDP dissociation inhibitor alpha and complement receptor 1.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

258
PO0735

Urinary Sphingolipids in Youth-Onset Diabetes

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Background: Sphingolipid metabolism is altered in diabetes has been implicated as a mediator of diabetic kidney disease (DKD). The purpose of this study was to evaluate urinary sphingolipids as an early marker of kidney injury in youth with type 1 (T1) and type 2 diabetes (T2DM).

Methods: A comprehensive panel of urinary sphingolipids, including sphingomyelin (SM), glucosylceramide (GC), ceramide (Cer), and lactosylceramide (LC) species, was performed in patients with youth-onset diabetes from the Treatment Options for Diabetes in Youth (TODAY) cohort. Sphingolipid levels, normalized to urine creatinine, were compared in 57 youth with T1DM, 59 with T2DM, and 44 healthy control subjects. The association of sphingolipids with early markers of DKD (albumin-to-creatinine [ACR] ratio and estimated glomerular filtration rate [eGFR]) was evaluated.

Results: The median age (IQR) of youth with diabetes was 22.2 years (19.9, 23.6) and the median duration of diabetes was 9.3 (8.5, 10.2) years. Urinary sphingolipid concentrations in youth with and without DKD (ACR > 30) were significantly elevated compared to healthy subjects (all p < 0.001). There were no significant differences between youth with type 1 and type 2 diabetes. All sphingolipid species were positively correlated with eGFR (all p < 0.001) and negatively with albumin-to-creatinine ratio (p = 0.001 for SM, Cer, GC; p = 0.0015 for LC). In multivariable analysis that adjusted for BMI and HbA1c, all urinary sphingolipid species remained significantly associated with eGFR (all p < 0.01). SM, GC, and Cer species remained independently associated with ACR (all p < 0.05).

Conclusions: Urinary sphingolipids are elevated in youth with diabetes and correlate with eGFR and albuminuria. Urinary sphingolipids may therefore represent an early marker of DKD.

PO0736

Long Non-Coding RNA Profiles and Declining Kidney Function in Patients with Diabetes and CKD

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Background: Long non-coding RNAs (lncRNAs) are endogenous molecules that are involved in gene regulation and play important roles in the pathogenesis of various renal diseases, including diabetic kidney disease (DKD). lncRNA signatures associated with DKD, however, have not been fully established. The objective of this study was to determine the whole blood lncRNA signature that is associated with increased risk of DKD progression.

Methods: Eighty-eight lncRNAs that were previously reported to be related to DKD were measured by quantitative PCR (qPCR) in RNA from whole blood (PAXgene RNA tubes) from 22 patients with type 1 diabetes and chronic kidney disease (12 of whom progressed to ESKD during 7-10 years of follow-up). GAPDH was used for sample normalization. We assessed declining kidney function as eGFR slope (mL/min/1.73m2/ year).

Results: Seventy-two of the 88 IncRNAs were detectable in more than half of the samples included in this study (n=11). Using Pearson’s test, eGFR slope was found to be significantly correlated with IncRNAs H19 (r=-0.56, P=0.0073) and CRNDE (r=-0.42, P<0.05). H19 and CRNDE were not correlated with HbA1c (r=-0.22, P=0.32 and r=-0.15, P=0.52 respectively), suggesting that these IncRNAs are associated with progression of DKD mediated by distinct pathways (independent of hyperglycemic condition).

Conclusions: We investigated plasma IncRNA profiles associated with declining kidney function in patients with diabetes. Although we need to confirm the results in an independent validation panel, our findings suggest that H19 and CRNDE are associated with declining kidney function and have potential to serve as circulating biomarkers for progression of DKD.

Funding: Commercial Support - Novo Nordisk
PO0737
A Comparison of PromarkerD to Standard-of-Care Tests for Predicting Renal Decline in Type 2 Diabetes

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Background: Diabetic kidney disease (DKD) can progress to end stage renal disease with associated increased morbidity and mortality. Current standard of care for assessments of DKD is measurement of estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR), but both tests have limitations. This study compared the biomarker-based PromarkerD test with SoC for predicting renal decline in community- based patients with T2D.

Methods: Baseline plasma biomarkers (CD5L, ApoA4, IgGfP5) measured by mass spectrometry were combined with clinical data (age, serum HDL-cholesterol, eGFR) using a validated algorithm to provide PromarkerD scores categorized as low, moderate or high risk in 857 participants with T2D from the Fremantle Diabetes Study Phase II. The 1st endpoint was incident DKD (reduction in eGFR to < 60 mL/min/1.73m^2) during follow-up) or eGFR decline ≥30%, in participants with baseline eGFR < 60 mL/min/1.73m^2. Logistic regression was used to compare the association of i) PromarkerD, ii) eGFR, iii) ACR, and iv) eGFR+ACR, with outcomes during 4 years of follow-up. Model performance was assessed by the ROC area under the curve (AUC).

Results: At baseline, participants (mean age 65 years, 54% males, median diabetes duration 7 years) had mean eGFR 82 mL/min/1.73m^2, geometric mean ACR 26 mg/g and were classified by PromarkerD as low (65%), moderate (15%) or high risk (24%) for renal decline. During 4.2±0.3 years of follow-up, 107 (13%) participants reached the 1st endpoint. PromarkerD had significantly higher predictive performance (AUC=0.88) compared to eGFR (0.82), ACR (0.63) and eGFR+ACR (0.82) (all P<0.001). Higher PromarkerD scores had a stronger association with the 1st outcome (odds ratio (OR) 3.26, 95% CI 1.22 to 9.1) per 1 SD increase compared to lower eGFR or higher ACR (OR=2.63 (2.13-3.23) and 1.21 (1.04-1.40) per 1 SD increase, respectively). PromarkerD remained significantly associated with the 1st outcome after adjusting for eGFR and ACR (OR=2.78 (1.9-3.53) per 1 SD increase). PromarkerD moderate and high risk scores were inversely prognostic for the 1st outcome (OR 8.11 and 21.34 versus low risk, respectively; both P<0.001).

Conclusions: PromarkerD outperformed the standard of care tests eGFR and ACR for predicting future renal decline in T2D.

Funding: Commercial Support - Proteomics International

PO0738
Urinary Interleukin 9 in Youth with Type 1 Diabetes Mellitus

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Background: Interleukin-9 (IL9) is a cytokine that promotes podocyte health in mice with Adamyricin-induced nephrotoxicity but its role in human kidney disease is uncertain. Glomerulosclerosis (GS) is a standard histologic measure of DS and has been used as a biomarker in DS research. The relationship between IL9 and GS or other clinical characteristics is unclear.

Methods: We performed an analysis of urine samples and clinical data from 104 youth with T1D (n=53). We measured ACR and used flow cytometry to count urinary podocyte-derived microRNPs (MMP/UCr) to measure a panel of cytokines implicated in diabetic nephropathy, including VEGF, TNFα and IL6, on the subjects were collected.

Results: The mean of age was 14±1.6 and 14±2.9 yrs. Mean HbA1c was 70.3±13.9 mmol/mol. The mean ACR was 3.1±9.0 mg/mmol with a mean eGFR of 140±36.2 mL/min/1.73 m^2. Regression was used to compare the association of i) PromarkerD, ii) eGFR, iii) ACR, and iv) eGFR+ACR, with outcomes during 4 years of follow-up. Model performance was assessed by the ROC area under the curve (AUC).

Conclusions: PromarkerD outperformed the standard of care tests eGFR and ACR for predicting future renal decline in T2D.

Funding: Commercial Support - Proteomics International

PO0740
Diabetes Mellitus Associates with Differences in the Metabolome of Patients with CKD

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Background: Diabetic Mellitus (DM), the most common cause of chronic kidney disease (CKD) and end stage kidney disease, worldwide. However, the pathogenesis of the poorly understood. We have sequenced, in an important tool to understand gene expression changes, protein level changes are poorly understood. SOMAscan is an emerging method that can robustly measure the level of thousands of proteins.

Methods: We have performed unbiased SOMAscan proteomics and quantified the amount of 1317 proteins in 24 snap frozen kidney tissues collected from nephrectomies. Our samples included 10 control healthy samples, 10 from subjects with overt DKD (CKD stage 3a), and 14 from subjects with late DKD (CKD stages 3b or 4). Demographic and clinical characteristics of the subjects were collected.

Results: The mean of age was 61±16 and 65% of the subjects were male. The median glomerular filtration rate (eGFR) was 108 (33) in control, 54 (5) in overt DKD, and 32 (28) in late DKD. We identified 279 proteins showing differences at overt DKD samples, and 381 proteins in late DKD samples compared to controls. Gene ontology analysis indicated enrichment for immune system and metabolic processes. The protein level of matrix metalloproteinase-7 (MMP-7) showed the strongest differences between control and DKD. Linear regression, adjusted for key co-variables identified 96 proteins whose levels were correlated with eGFR, including cystatin C and MMP-7. We observed a moderate correlation between transcript and protein levels (r = 0.43, p < 2.2e-16).

Conclusions: SOMAscan proteomics identified important changes in protein expression in overt and late DKD, these could serve as important biomarkers or therapeutic targets.

Funding: NIDDK Support
Conclusions: We have identified significant differences in the metabolome of CKD patients with well-controlled DM compared to those without DM. Further research is needed to evaluate the potential role of these metabolic pathways and if they contribute to the high morbidity and mortality burden in CKD patients with DM.
Funding: NIDDK Support, Veterans Affairs Support

PO0741
Urinary Biomarkers and ESKD Risk in Persons with Diabetes and CKD
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Background: Tubulointerstitial damage is a feature of diabetic CKD, but correlates poorly with eGFR and albuminuria. Urine biomarkers of kidney tubule health may be independently associated with risk of ESKD in diabetic CKD.

Methods: We identified 1,145 participants from the REGARDS study with baseline eGFR≥60 mL/min/1.73m2 and diabetes. Per case-cohort design, we randomly selected a subcohort of 360. Within the subcohort there were 93 ESKD cases; we further sampled all remaining ESKD cases not included in the subcohort (N=68). These 161 ESKD cases were identified by USRDS linkage over mean follow-up of 4.3±2.7 years. In baseline urine samples, we measured biomarkers of kidney tubule injury (kidney injury molecule-1 [KIM-1]), inflammation and fibrosis (monocyte chemoattractant protein-1 [MCP-1]; chitinase-3-like protein [YKL-40]), function (alpha-1-microglobulin [α1m]; uromodulin [UMOD]), and cell repair (epidermal growth factor [EGF]). Using weighted Cox models, we calculated hazard ratios (HR) of ESKD by baseline biomarkers. LASSO regression retained KIM-1 (HR per doubling=1.31 [1.06-1.62]) and MCP-1 were each associated with higher ESKD risk. Strengths of association were of comparable magnitude to urinary albumin (Table). LASSO regression retained KIM-1 (HR per doubling=1.31 [1.06-1.62]) and α1m (HR per doubling=1.36 [1.08-1.70]) as most strongly associated with ESKD.

Results: Subcohort participants had mean age 70±9 years, 47% male, 53% Black, mean eGFR=60±3 mL/min/1.73m2 and median A1C=7.6 (IQR 6.6-8.8). Adjusting for baseline eGFR and albuminuria, higher KIM-1, α1m, and MCP-1 were each associated with higher ESKD risk. Strengths of association were of comparable magnitude to urinary albumin (Table). LASSO regression retained KIM-1 (HR per doubling=1.31 [1.06-1.62]) and α1m (HR per doubling=1.36 [1.08-1.70]) as most strongly associated with ESKD.

Conclusions: Among persons with eGFR≥60 mL/min/1.73m2 and diabetes, urine KIM-1 and α1m captured the influence of kidney tubule health on longitudinal risk of ESKD. These biomarkers may facilitate identification of persons with kidney disease and diabetes at greatest risk of ESKD.
Funding: NIDDK Support

Adjusted HR per doubling of individually-modeled urine biomarkers with ESKD

PO0742
The Potential Value of Urinary Extracellular Vesicles VEGF-A165b in Diagnosis of Diabetic Kidney Disease
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Background: Novel biomarkers are needed for management of diabetic kidney disease (DKD). Urinary extracellular vesicles (uEVs) were served as an ideal resource of biomarkers in kidney disease. VEGF-A165b is an angiogenic factor secreted from podocytes correlated with DKD. This study was aimed to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Methods: Urine samples were collected from 36 patients with T2DM and 12 controls. Subjects with T2DM were stratified into three groups according to UACR, eGFR, and T2DM duration. Two groups had T2DM duration ≥5 years, and one group had T2DM duration ≤5 years. ROC curve was used to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Results: Urinary MVs and exosomal VEGF-A165b were higher in T2DM with ACR>300mg/g than those with ACR<30mg/g. In addition, urinary MVs and VEGF-A165b were higher in patients with ACR≥300mg/g than those with ACR<30mg/g, and exosomal VEGF-A165b levels were lower in patients with ACR≥300mg/g than whose ACR<30mg/g. Furthermore, VEGF-A165b in uEVs increased with the DM duration. VEGF-A165b in patients with duration longer than 10 years were higher than whose duration was less than 5 years. Correlation analysis revealed eGFR was negatively correlated with urinary MVs and exosomal VEGF-A165b. ROC curve showed that AUROC of urinary MVs and exosomal VEGF-A165b for the diagnosis of DKD were 0.9091 and 0.8269. IHC revealed that VEGF-A165b was elevated in renal tubules in STZ-induced DM rats.

Conclusions: A increased level of uEVs-VEGF-A165b was observed in DKD patients and was correlated with decline of eGFR. uEVs-VEGF-A165b may be used as a promising biomarker reflecting the severity of DKD and may suggest a pathological role in the development of the disease.

PO0743
Independent Predictive Factors of Estimated GFR Decline in Type 2 Diabetes Patients with Preserved Kidney Function
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Background: We examined predictors of annual decline in estimated glomerular filtration (eGFR) in patients with type 2 diabetes and preserved kidney function.

Methods: In a prospective, observational cohort study, 392 Japanese patients with type 2 diabetes and baseline eGFR ≥ 60 mL/min/1.73m2 were followed over one year (mean period 5.5 years; IQR 3.9–7.3). Linear regression was used to estimate participants’ annual decline rate in eGFR over time. We defined subjects with an annual eGFR decline ≥ 5% per year as rapid progression and eGFR decline < 5% as slow progression. In addition, time-averaged values of each laboratory data were calculated and used for sensitivity analysis.

Results: The study population had a median age of 59.0 years (IQR, 53.0–64.0) and 75% were male. The median duration of diabetes was 15.9 years (IQR, 11.2–20.4). During the follow-up period, 46 (11.7%) patients had a rapid decline in eGFR (median decline -6.51%; IQR, -8.59--5.60). Compared to patients with a slow decline in eGFR (N = 346), those with a rapid decline in eGFR had significantly higher HbA1c levels and lower HDL-cholesterol (HDL-c) levels at baseline. Multivariable logistic regression models revealed...
that lower baseline hemoglobin and HDL-c levels were independent predictors of annual decline in eGFR. OR, 0.69; 95% CI, 0.53–0.89; P = 0.005; respectively). Furthermore, time-averaged hemoglobin and HDL-c levels were also independent predictors of annual decline in eGFR (OR, 0.62; 95% CI, 0.46–0.82; P < 001; OR, 0.97; 95% CI 0.94–0.99, P = 0.007, respectively).

Conclusions: Our findings highlight the important effect of lower hemoglobin and HDL-c levels as independent predictors of rapid decline in eGFR in patients with type 2 diabetes and preserved kidney function.

PO0744
Post-Hospitalization Blood Pressure (BP) and Diabetes (DM) Control and Outcomes in Patients with Diabetic Kidney Disease (DKD)
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Background: DKD is the most common cause of ESKD in the US but because the course of progression is prolonged, research to elucidate risks and effective interventions are difficult. In a high-risk cohort with DKD, do post-hospitalization BP and DM control act as good surrogate markers for outcomes?

Methods: Using Looking Glass, Montefiore Medical Center’s clinical database, we created a cohort of patients with a first discharge in 2016 who met the following criteria: CKD stage 3b or 4 and Proteinuria >300 and <5000mg/gm. Follow up data regarding CKD outcomes up to 2 years, clinic visits, RAASI prescriptions, mean systolic BP (SBP) and HgbA1c levels within 1 year of discharge were collected. Cox proportional hazards was used in adjusted analyses, to estimate the HR of mean SBP and HgbA1c levels, both dichotomized at the 75th percentile, with ESKD incidence or death over 2 years of follow-up.

Results: A total of 572 individuals met DKD criteria and had a first discharge in 2016. The mean age for the cohort was 66.8 years (SD 11.5), 244 (42.7%) were male, 224 (39.3%) were Black, 210 (36.8%) were Hispanic and 33 (5.8%) were White. Sixty-eight percent had a readmission within 1 year of discharge with median time to readmission at 63 days (IQR 22-149). Ninety-three percent of individuals had an outpatient clinic visit and the median number of clinic visits was 30 (IQR 16-47) over 1 year, with median time from discharge to an outpatient visit of 8 days (IQR 4-18). Mean SBP was 138±19mmHg (SD 22.2) with 26.9% of individuals with a mean SBP >150mmHg during 1 year of follow up. Mean HgbA1c was 8.6 (SD 2.1) with 192 (33.6%) who had HgbA1c >9.7 (SD 2.2) with 26.9% of individuals with a mean SBP >150mmHg during 1 year of follow up. Mean HgbA1c was 8.6 (SD 2.1) with 192 (33.6%) who had HgbA1c >9.7 over 1 year of follow up. Eighty-eight (15.4%) patients died and 99 (17.3%) progressed to ESKD over 2 years of follow up. In models adjusting for age, sex and race/ethnicity there was a positive association between SBP >150 (HR 1.53, 95% CI 1.12-2.09) and HgbA1c >9.7 (HR 1.58 95% CI: 1.16-2.15) and time to ESKD or death.

Conclusions: High mean BP and HgbA1c levels during 1 year post-discharge are associated with adverse outcomes in a cohort of hospitalized patients with DKD. These measures serve as useful surrogate biomarkers to study DKD interventions in a high-risk population.

PO0745
Finerenone Dose-Exposure-UACR Response Analyses of FIDELIO-DKD Phase 3 and the Effect of SGLT-2 Inhibitor Co-Medication
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Background: The mineralocorticoid receptor antagonist finerenone and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce albuminuria and the risk of kidney failure. The combination of these therapies holds promise to augment nephroprotection through activation of different pathways. Model-based approaches considering individual dosing and exposure and correcting for covariates can support streamlined conclusions than stratification for baseline comedication. We developed a population pharmacokinetic/pharmacodynamics (popPKPD) model to assess the finerenone dose-exposure-response relationship for urine albumin-to-creatinine ratio (UACR) and the impact of combined SGLT2i-finerenone use on UACR.

Methods: We analysed 37296 UACR measurements in 5674 patients (549 patients with any recorded SGLT2i use) using nonlinear mixed-effects popPKPD modelling considering individual drug exposure. The model was used to characterize the trajectory of UACR progression over time, the exposure-response relationship of finerenone on UACR and the effect of SGLT2i.

Results: The popPKPD model described the observed UACR data well, with a proportional UACR progression over time, an indirect power model for the exposure-response relationship of finerenone and a constant effect of SGLT2i use. SGLT2i use did not modify finerenone efficacy (p=0.25) and indicated with 95% confidence that finerenone is at least 94.1% as efficacious in reducing UACR in patients using SGLT2i (Figure 1).

Conclusions: We successfully developed a popPKPD model that adequately described the dose-exposure-response of finerenone on UACR. The results demonstrated additive effects of SGLT2i on top of finerenone.

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KidneyIntelX as an Enrichment Tool for Clinical Trials in Early Diabetic Kidney Disease

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Background: Clinical trials in nephrology are often enriched for patients with high levels of albuminuria to increase event rates. KidneyIntelX is a composite risk score that incorporates plasma biomarkers and clinical data to predict progression of diabetic kidney disease. We sought to assess the value of KidneyIntelX for future clinical trials in patients with type 2 diabetes and normo- or microalbuminuria.

Methods: Plasma TNFR-1, TNFR-2, and KIM-1 were measured on the Renalytix KidneyIntelX platform in participants in the CANVAS trial with UACR <300 mg/g (n=3277). A logistic regression model incorporating the 3 biomarkers and clinical variables was applied to obtain the predicted probabilities for a composite kidney outcome (n=3277). A total of 14,543 participants from the CANVAS Program (N = 10,142) and CREDENCE (N = 4,401) were included. Among participants with baseline eGFR measurements, 1919 (13.2%) had eGFR <45 mL/min/1.73 m², 2972 (20.4%) had eGFR 45-60 mL/min/1.73 m², and 9649 (66.3%) had eGFR >60 mL/min/1.73 m². CANA delayed the time to first doubling of SCr event and first ESKD event relative to PBO (P = 0.78; Figure). Reduced risk of ESKD was also seen with CANA versus PBO (HR, 0.69; 95% CI, 0.55–0.87), irrespective of baseline eGFR (interaction P = 0.86).

Conclusions: In patients with T2DM and high CV risk or nephropathy, CANA reduced the risk of doubling of SCr and ESKD, with consistent benefits observed across baseline chronic kidney disease stage, including those with preserved eGFR >60 mL/min/1.73 m².
PO0749

Phase Ib Study of the Soluble Guanylate Cyclase Activator BI 685509 in Patients with Diabetic Kidney Disease

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Background: Soluble guanylate cyclase (sGC) plays a key role in the kidney nitric oxide–cyclic guanosine monophosphate (NO-cGMP) pathway. Increased albuminuria is associated with kidney function loss. The NO-independent sGC activator BI 685509 assessed the safety and efficacy of BI 685509 in patients with diabetic kidney disease and albuminuria.

Methods: This placebo (PBO)-controlled, multiple dose study enrolled patients with type 1 or 2 diabetes, estimated glomerular filtration rate (eGFR) 20–75 mL/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m² and urinary albumin creatinine ratio (UACR) 20–75 mg/min/1.73m². Patients were randomised to three active dose groups receiving oral BI 685509 (tested doses after titration: 1 mg three times daily [TID], n=20; 3 mg once daily [QD], n=19; 3 mg TID, n=20) or PBO (n=15) for 28 days. Efficacy was assessed by the proportion of responders, defined as patients with a ≥20% decrease from baseline in UACR measured in first morning void (UACR₁₄₄₈) and 10-h (UACR₉₉₆₄) (PBO, 3 mg QD and 3 mg TID only) urine.

Results: At baseline, median eGFR was 47.0 mL/min/1.73m² and median UACR₉₉₆₄ was 641.5 mg/g, although this varied between groups. Drug-related adverse events (AEs) occurred in 12 patients (16.2%; BI 685509 15.3%, PBO 20.0%); the most frequent were hypotension (4.1%) and diarrhoea (2.7%). AEs leading to discontinuation occurred in 4 patients (5.4%; BI 685509 5.1%, PBO 6.7%). Compared with PBO, the proportion of patients receiving BI 685509 classed as responders was higher (Figure).

Conclusions: BI 685509 treatment was generally well-tolerated with over 50% of patients in the 3 mg QD and 3 mg TID dose groups appearing to show a response in UACR₁₄₄₈.

Funding: Commercial Support - Boehringer Ingelheim

PO0750

Comparative Effectiveness of SGLT-2 Inhibitors, DPP-4 Inhibitors, and GLP-1 Agonists in US Veterans with and Without CKD

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Background: Recent clinical trials have shown that SGLT2 inhibitors (SGLT2i) vs. placebo substantially reduce the risk of eGFR decline, ESRD, and renal-CV-related mortality in CKD patients. However, little is known about the comparative effectiveness of SGLT2i vs. other newer anti-diabetic medications (DPP-4 inhibitors [DPP4i], GLP1 agonists [GLP1a]) on CKD outcomes using real-world data in patients with and without CKD.

Methods: In US Veterans with diabetes receiving care from the VA healthcare system over 2004-18, we identified incident (new) users of SGLT2i vs. DPP4i vs. GLP1a therapy, excluding combined users of the examined classes. In analyses stratified by presence vs. absence of CKD defined by eGFR and albuminuria levels, we examined associations of SGLT2i vs. DPP4i vs. GLP1a use with the composite outcome of incident ESRD+all-cause death using multivariable Cox models.

Results: In 64,564 patients who met eligibility criteria, 51% patients had CKD, and 8%, 77%, vs. 15% were new users of SGLT2i, DPP4i, vs. GLP1a, respectively. Patients contributed a total of 182,177 person-years of follow up, during which 10,861 incident ESRD/death events were observed (crude rate 59.6 events/1000 person-years). Median (IQR) at-risk time was 2.1 (0.9, 4.0) years. Compared to DPP4i, use of SGLT2i was associated with lower risk of the composite outcome across all Cox models (adjusted HR [95%CI] 0.86 [0.75-1.00]). The beneficial association of SGLT2i use with the composite outcome was limited to patients with pre-existing CKD. Across all cohorts (overall, CKD, non-CKD), GLP1a did not show comparable risk of the composite outcome when compared to DPP4i in adjusted analyses.

Conclusions: In a national cohort of US Veterans with diabetes, SGLT2i use was associated with lower risk of the composite outcome of ESRD+all-cause mortality in CKD patients, yet had comparable risk to DPP4i in those without CKD. Further studies are needed to determine the long-term safety and effectiveness of novel anti-diabetic medications using real-world data.

Funding: Veterans Affairs Support
due to DRAEs. Changes seen in SBP did not differ between PBO and BI 685509 dose groups. Compared with PBO, the proportion of patients receiving BI 690517 classified as responders was higher for UACR_{min} (PBO 37.5% vs 3 mg/161.1, 10 mg 53.8; 40 mg 80.0%) but similar for UACR_{max} (PBO 50.0% vs 10 mg 50.0%, 40 mg 60.0%).

**Conclusions:** BI 690517 was generally well tolerated and appears to have an early effect on UACR, with over 50% of treated patients being classified as responders. These data need to be confirmed in larger studies.

**Funding:** Commercial Support - Boehringer Ingelheim

**PO0752**

A Comparison of the Renal Composite Outcome Between Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide 1 Receptor Agonists in Japanese Diabetes Patients

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Background: the renal outcome benefit in some large-scale clinical trials has been met with skepticism due to not only sodium-glucose co-transporter 2 inhibitors (SGLT2i) but also glucagon-like peptide 1 receptor agonists (GLP1Ra) in patients with type 2 diabetes mellitus (T2DM). However, there is not enough evidence of direct comparison between these drugs in clinical practice.

**Methods:** We retrospectively built two databases of T2DM patients who were visiting members of the Kanagawa Physicians Association. One database consisted of T2DM patients who were administered SGLT2i and the other of T2DM patients who were administered GLP1Ra for more than a year. We compared the renal composite outcome of 541 SGLT2i-treated patients without the concomitant use of GLP1Ra and 265 GLP1Ra-treated patients without the concomitant use of SGLT2i. We have set the renal composite endpoint as the progression of the stage of albuminuria or the decrease of estimated glomerular filtration rate (eGFR) by a 15% per year. For comparative analyses, we built the cohort model of patients treated with SGLT2i or GLP1Ra, using a propensity score-matching method with the following algorithm: 1:1 nearest neighbor match with a ±0.036 caliper and no replacement.

**Results:** The comparison of 134 propensity-matched patients in each group was performed. The median values of the age, body mass index, eGFR, ACR, and duration of treatment when both groups were combined were 64.0 years, 26.9, 71.1 mL/min/1.73 m², 29.8 mg/gCr, and 36 months, respectively. The incidence of renal composite outcome was significantly lower in SGLT2i treated patients than in GLP1Ra treated patients (n = 15 [11%] and n = 27 [20%], respectively, p = 0.001 by McNemar’s test). The estimate hazard ratios and robust 95% confidence intervals (CI) for the renal composite outcome by the analysis of cox proportional hazards models were 0.69 (95% CI, 0.53, 0.90; p = 0.006) in SGLT2i treated patients. There was a significant difference in the annual change in eGFR between the two groups: 0.8 ± 5.1 % in SGLT2i treated patients and -3.4 ± 7.0 % in GLP1Ra treated patients (p = 0.0049).

**Conclusions:** By this retrospective study, SGLT2i treatment has shown more preferable influence on the change of eGFR than GLP1Ra treatment in Japanese T2DM patients.

**PO0753**

Role of β2-Adrenergic Receptor Agonists in the Treatment of Diabetic Nephropathy

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**Background:** Diabetes is the leading cause of end stage kidney disease (ESKD) and affects podocytes. We previously showed in cells and mice that pharmacological activation of mitochondrial biogenesis by the long-acting β2-AR agonist formoterol contributes to podocyte recovery from injury.

**Methods:** We examined the association between COPD, in which the vast majority of patients receive β2-AR agonists, and CKD progression in a national cohort created from patient records within the Veterans Health Administration (VHA). Cohort members were limited to age 65 to 85 years with stage 3 CKD defined based upon ICD-9 codes (ICD-9: 416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8). Veterans entered the cohort in 2010 and were followed through 2016. We are also currently testing the efficacy of formoterol in restoring glomerular function in type I (streptozotocin) and type 2 (high fat diet) diabetic murine models.

**Results:** Of 392,539 Veterans with stage 3 CKD in 2010, 4,727 progressed to stage 5 CKD by 2016. The age- and sex-adjusted odds ratio for the association between baseline COPD and progression to stage 5 CKD was 0.89 (95% CI: 0.83, 0.96), indicating that Veterans with COPD at baseline had lower odds of progression to stage 5 CKD than Veterans without COPD at baseline.

**Conclusions:** Our large retrospective cohort study suggests that β2-AR agonists slow the progression of CKD. Given that diabetes is the most common cause of ESKD, the effect of β2-AR agonists on progression of CKD is likely driven by the effect on diabetic nephropathy. Animal studies to directly test this hypothesis are underway.

**Funding:** NIDDK Support, Veterans Affairs Support

**PO0754**

Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Network Meta-Analysis of Randomized Controlled Trials

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**Background:** Previous studies have reported that sodium-glucose co-transporter 2 (SGLT2i) inhibitors affect electrolyte levels in patients with type 2 diabetes (T2D).

**Methods:** We systematically searched PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov up to through January 2021 to identify eligible randomized controlled trials (RCTs) that reported the mean changes in serum electrolytes, including magnesium, sodium, potassium, phosphate, and calcium. We performed both random-effects pairwise and network meta-analyses to calculate the weighted mean difference (WMD) and 95% confidence intervals (CI).

**Results:** In total, we included 26 RCTs involving 28,943 T2D patients with 6 SGLT2i. Compared with the placebo, SGLT2i were significantly associated with elevations in serum sodium by 0.7 mmol/L (95% CI: 0.10, to 0.88 mmol/L) and serum phosphate by 0.02 mmol/L (95% CI: 0.01 to 0.03 mmol/L). Our network meta-analysis showed no evidence of significantly superior efficacy of any specific SGLT2 inhibitor over the others, although dapagliflozin was associated with a larger magnitude in significant increase uses in serum magnesium associated with dapagliflozin (WMD = 0.03 mmol/L, 95% CI: 0.01, to 0.05 mmol/L). Similarly, no statistically detectable differences were evident between any two of SGLT2 inhibitors on serum levels of other electrolytes.

**Conclusions:** SGLT2i could significantly increased serum magnesium and phosphate levels, consistent with a class effect of SGLT2 inhibition. However, further investigation on more data for long-term efficacy and safety in T2D patients with different clinical phenotypes are needed for further investigation.

**PO0755**

Association of Fibrate Use with Cardiovascular Disease Mortality Across CKD Stages

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**Background:** Elevated serum lipids are risk factors for cardiovascular disease (CVD) in the general population and common first-line treatment includes fenofibrate for those with high triglycerides (TG) or low high-density lipoproteins (HDL). Recent studies have suggested that fibrates may be beneficial for CVD death outcomes in those with chronic kidney disease (CKD). Yet how the relationship between fibrates and early CVD death differs across CKD stages remains uncertain.

**Methods:** In male Veterans with adverse lipid levels (TG ≥150 mg/dL or HDL ≤40 mg/dL), initial fibrate users and non-users were matched on CKD stage, TG and HDL levels. The cohort of 233,082 patients were followed until 2014. We used inverse probability weighting in the fitting of marginal structural models to adjust for time-varying confounding and informative censoring in investigating the average direct effect of fibrate use (reference: non-use), with 24-month cardiovascular mortality. Models were stratified by CKD stage, diabetes status, and baseline sodium, potassium, calcium, and phosphorus levels.

**Results:** Patients were a mean±SD age of 62±12 years, and 26% of patients had CKD or end-stage renal disease (ESRD). The median[IQR] of baseline TG and HDL were 310[220,436], and 34[30, 40] mg/dL, respectively. Across all baseline CKD stages, the use of fibrates was associated with a decrease in CVD death compared to non-users. These associations gradually declined across advancing CKD stages, where patients with ESRD on renal replacement therapy had the lowest observed risks (Hazard Ratio[95%CI]: 0.54[0.34, 0.87]) [Figure 1].

**Conclusions:** Fibrates use was associated with lower CVD mortality. These risks varied across CKD stage, but those with ESRD tended to have better CVD death outcomes. Additional studies are imperative to better tailor lipid therapy and management against adverse outcomes among the late-stage CKD and ESRD patients.

**Funding:** Veterans Affairs Support

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Underline represents presenting author.
PO0756

Effect of CKD Stage on Myocardial Infarction Risk with Niacin Use in Male Veterans
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Background: Niacin is a lipid therapy shown to have cardio-protective effects, particularly in those with high triglyceride (TG) and low high-density lipoprotein (HDL) levels. But, in chronic kidney disease (CKD) patients who have elevated risk of cardiovascular risk and altered lipid levels, it remains unclear if CKD stage impacts these associations.

Methods: In males with worse lipid levels (TG≥150 mg/dL or HDL≤40 mg/dL), we matched patients with an incident niacin prescription to non-niacin users on CKD stage, TG and HDL levels. In this study of 336,178 niacin users and non-users, we evaluated the relationship of time-varying niacin use with 24-month myocardial infarction (MI) hospitalization. Cox models included adjustment for time-varying covariates and were stratified by baseline CKD stage.

Results: Patients were a mean 64 years old, with a median[IQR] of TG and HDL of 203[143, 297] and 34[29, 39] mg/dL, respectively. In unadjusted models, non-CKD, CKD 4/5 and end-stage renal disease (ESRD) niacin users had higher risks of a MI hospitalization, yet CKD 3A-3B patients had null risks, compared with non-users. With adjustment for case-mix variables, including comorbidities, we observed a linear relationship across baseline CKD stages, where risks progressively increased with worse stage. Non-CKD niacin users had lowest risks of 24-month MI hospitalization, while both CKD 4/5 and ESRD patients trended towards elevated risks of event. The relationships between niacin use and MI hospitalization remained the same with adjustment for laboratory and other lipid.

Conclusions: In time-varying analyses, niacin use was associated with lower risks of 24-month MI hospitalization in non-CKD and CKD 3A patients. The risks of MI hospitalization were progressively elevated with worse CKD stages. Additional studies are needed to further examine the relationship between lipid modulating therapies in the context of CKD patients.

Funding: Veterans Affairs Support

PO0757

Advantages of Metformin for the Prevention and Mitigation of Diabetic Foot Ulcer in Diabetic Kidney Disease from a Large-Scale, Real-World Cohort
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Background: Diabetic foot ulcer (DFU) and diabetic kidney disease (DKD) are diabetes-related microvascular complications strongly correlated with high morbidity and mortality. Metformin potentially confers a wound-healing advantage, although there are no well-established evidence. We first time investigated the effect of metformin on DFU among large retrospective cohort of DKD.

Methods: This retrospective cohort study enrolled DKD patients from two South Korean tertiary-referral centers. Primary outcomes were all-cause mortality and DFU events; secondary outcomes included hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade ≥3. Multivariate cox analysis and Propensity score matching (PSM) was used to balance baseline intergroup differences between metformin users and metformin non-users.

Results: Among 10,832 patients (4,748 metformin non-users), the 117.5±66.9 months follow-up period, all-cause mortality rate and DFU incidence were, 37.1%, and 5.2%, respectively. Fully adjusted multivariate Cox analysis showed that metformin users had a lower all-cause mortality (adjusted hazard ratio 0.63; 95% confidence interval 0.58–0.68; p<0.001) and DFU events (0.39; 0.31–0.8; p<0.001) and DFU events (0.39; 0.31–0.8; p<0.001). After PSM, metformin users showed lower all-cause mortality (0.61; 0.55–0.67; p<0.001), DFU events (0.42; 0.32–0.56; p<0.001), and secondary outcomes (hospitalization, amputation, composite of amputation or vascular intervention, and DFU with Wagner Grade ≥3). Table).

Conclusions: Metformin therapy in DKD patient can lower all-cause mortality, DFU incidence, and DFU progression.

Survival analysis of primary and secondary outcomes

Gaps in CKD Awareness Among People with Type 2 Diabetes

Background: Diabetes is one of the most common causes of chronic kidney disease (CKD) in adults, with around 1 in 3 people with diabetes also living with CKD. Clinical guidelines recommend annual screenings of urinary albumin and glomerular filtration rate for people with type 2 diabetes (T2D). Previous studies have identified low awareness, testing and diagnosis of CKD among people with T2D and their healthcare providers (HCP). By drawing comparisons to cardiovascular disease (CVD), the present study aimed to assess awareness of CKD, renoprotective diabetes therapies, and kidney health metrics among people with T2D.

Methods: In February 2021, 1021 people with T2D from the dQ&A Patient Panel responded to an online survey assessing perceptions, knowledge, HCP engagement, and lifestyle behaviors related to CKD and CVD. Respondents received $10 USD for completing the survey. Data was collected with Qualtrics, prepared with IBM SPSS, and analyzed in MarketSight.
Results: Awareness of the link between T2D and CKD was lower than awareness of the link between T2D and CVD; 57% of respondents strongly agreed that having T2D increases the risk of CKD, compared to 63% who strongly agreed that T2D increases the risk of CVD. The percentage of respondents who often consider their personal risk of CKD (19%) was also lower than for CVD (26%). Awareness of renoprotective and cardioprotective therapies was low overall. While 37% were aware that some T2D drugs are cardioprotective, only 22% were aware of renoprotective benefits. Respondents on SGLT-2 inhibitors or GLP-1 agonists were more likely to be highly aware of their cardioprotective benefits than their renoprotective benefits (52% vs. 30% for SGLT-2 users and 45% vs. 31% for GLP-1 users). Knowledge of personal metrics for glomerular filtration rate for real health indicators, eGFR (38%), and uACR (26%), lagged behind knowledge of diabetes and CVD metrics: weight (100%), A1C (98%), blood pressure (94%), and cholesterol (75%). Only 41% of respondents had discussed their CKD risk with a diabetes-related HCP, but those who had were more likely to be aware of CKD risk and therapies.

Conclusions: This data highlights a gap between T2D patients’ awareness of CKD risks and protective therapies and those of CVD. To prevent CKD and improve outcomes, this study emphasizes the need for better patient education on CKD’s connection to T2D.

Funding: Commercial Support - AstraZeneca

PO0759

Feature Selection and Machine Learning Modeling for Predicting Diabetic Kidney Disease Risk in Asians

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Background: Machine learning (ML) techniques may improve disease prediction and interpretability of regression models by identifying the most relevant features in multi-dimensional data. We evaluated the ability of various ML classifiers for feature identification and improving the prediction accuracy of diabetic kidney disease (DKD).

Methods: We utilized longitudinal data from 1364 Chinese, Malay and Indian participants aged 40-80 years with diabetes but free of DKD who attended the baseline visit of the Singapore epidemiology of Eye Diseases Study in 2004-2011 and were followed up for 6 years (2011-2017). Incident DKD (n=162) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2 or 25% decrease in eGFR at follow-up. We evaluated 339 features including demographic/clinical, retinal imaging, genetic and serum metabolomics profile and tested nine ML algorithms along with feature selection (gradient boosting decision tree, elastic net, support vector machine, neural network, LASSO etc.). The performance of the best ML model based on optimum features was compared to that of logistic regression (LR) with traditional risk factors using the area under the receiver operating characteristic curve (AUC), sensitivity and specificity.

Results: The best performing model was a combination of Recursive feature elimination (RFE) for variable selection and Elastic Net (EN) using 15 predictors from demographic/clinical +metabolite set with AUC, sensitivity and specificity of 0.852, 83.00% and 73.5% compared to 0.796, 83.00% and 61.88% by LR. The top-15 predictors of DKD risk included seven risk factors and eight metabolites: age, antidiabetic medication use, presence of hypertension, diabetic retinopathy, higher levels of systolic blood pressure, HbA1c, lower levels of eGFR, higher levels of triglycerides in IDL, phospholipids in chylomicrons and medium VLDL, total cholesterol in chylomicrons and very small VLDL, medium LDL, cholesterol esters in very large HDL and lower levels of DHA, lactate and acetate.

Conclusions: ML together with feature selection improved prediction accuracy of DKD risk in the general population with diabetes and identified novel risk factors including metabolites.

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PO0760

Risk Score to Predict CKD Among Mexican Individuals with Diabetes Mellitus

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Background: The two major causes of CKD are type 2 diabetes (T2D) & hypertension, which are responsible for up to two-thirds of the cases. More than half of patients in Mexico with incident ESRD have an underlying diagnosis of T2D. Some prediction models have been developed for the purposes of screening CKD & its progression. However, their generalizability to the Mexican population is not known, & few have been validated in different populations & rarely in LMIC. We aimed to develop & validate a lab and office-based risk prediction scores for CKD among Mexican patients with T2D.

Methods: The prospective cohort consisted of 105,310 patients enrolled in the Integral Management of Diabetes by Stages program. 18,148 patients were randomly assigned to the training & testing sets based on an 80-20 ratio. Logistic regression models were used to assess risk factors for CKD. A stepwise selection process was performed to determine the best predictive equations.
PO0762
Using Machine Learning to Predict CKD upon Type 2 Diabetes Mellitus Diagnosis
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Background: Chronic kidney disease (CKD) accounts for the majority of increased risk of mortality for diabetic patients, manifesting in approximately half of patients diagnosed with type 2 diabetes mellitus (T2DM). Although increased screening frequency can avoid missed diagnoses, this is not implemented uniformly. We developed and retrospectively validated a machine learning algorithm (MLA) to predict CKD within 5 years upon T2DM diagnosis.

Methods: Electronic health records (EHR) data of 171,201 recently diagnosed T2DM patients (age 18) was extracted from a proprietary database of >700 healthcare sites across the US between 2007-2020. A random forest MLA was developed to assess risk of Stage 3+ CKD (CKD 3+) in T2DM patients using EHR data collected in the year prior to T2DM diagnosis. International Classification of Diseases codes (ICD-9 and ICD-10) were used to identify T2DM and CKD 3+ patients. The MLA was tested on a hold-out test set of 42,801 patients as well as a separate external validation dataset. The Centers for Disease Control and Prevention (CDC) CKD risk score was used as a hold-out test set and the external validation dataset via area under the receiver operating characteristic curve (AUROC).

Results: On a hold-out test set and an external validation dataset, the MLA outperformed the CDC CKD risk score when analyzed for prediction of CKD 3+ in T2DM patients (Fig 1).

Conclusions: This retrospective study shows that a MLA can provide timely predictions of CKD among recently-diagnosed T2DM patients. Early detection of CKD in diabetic patients may enable timely therapeutic interventions, lifestyle changes, prevention of progression, and reduction of dialysis dependency, as well as healthcare costs.

Figure 1. Area under receiving operating characteristic curves for the machine learning algorithm (MLA) and CDC CKD risk model (CDC) for Stage 3+ diabetic CKD predictions performed on the hold-out test set and external validation dataset.

PO0763
Contemporary CKD Incidence Rates in Diabetes by Race/Ethnicity, Sex, and Age
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Background: Diabetes is the most common cause of chronic kidney disease (CKD), yet little is known about current CKD incidence rates and demographic predictors in these patients. The study aim was to estimate CKD incidence over time in adults with diabetes treated in two large healthcare systems.

Methods: The Center for Kidney Disease Research, Education, and Hope registry data is curated from electronic health records at Providence St. Joseph Health and University of California Los Angeles Health. Age, sex, and race/ethnicity adjusted CKD incidence rates were calculated over two-year time periods covering 2014–2019. CKD was identified by ≥2 laboratory measures (estimated glomerular filtration rate <60 mL/min/1.73m², urine albumin/creatinine ratio ≥30 mg/g, urine protein/creatinine ratio ≥150 mg/g) a90 days apart or administrative codes. Diabetes was identified by laboratory measures (HbA1c, blood glucose), use of glucose-lowering medication, or administrative codes.

Results: The overall CKD incidence (95% CI) rate in diabetes declined from 109.1 cases/1000 person-years (106.1–112.1) in 2014-15, to 104.2 cases/1000 person-years (101.7–106.8) in 2016-17, to 96.0 cases/1000 person-years (93.5–98.5) in 2018–19 (p<0.001 for trend, Figure). CKD incidence only declined in Whites over these time periods. CKD incidence rates were lowest in Whites and Asians and highest in American Indians/Alaska Natives (AI/AN) and Native Hawaiians/Pacific Islanders (NHPI). CKD incidence rates were higher in men than women and increased with age.

Conclusions: CKD incidence has recently declined in patients with diabetes overall, and specifically among Whites. AI/AN and NHPI patients with diabetes had the highest rates of CKD incidence. Studies of targeted strategies in high-risk populations will be important to prevent CKD.

Funding: Other U.S. Government Support

Figure.
Results: There was no difference between groups in the mean (SD) age (T1D: 58 (14) years; CONs: 56 (15) years; p=0.82) or in the gender distribution (33% female in both groups, p<1). Participants with T1D had a mean duration of diabetes of 38 (18) years, a higher median fasting plasma glucose (FPG) (T1D: 150 (60) mg/dl; CONs: 100 (30) mg/dl; p<0.01) and a lower mean estimated glomerular filtration rate (eGFR) (T1D: 73 (32) ml/min/1.73m²; CONs: 88 (15) ml/min/1.73m²; p=0.12), although not significantly for the latter. There were no significant differences between groups in renal cortical R₂ (T1D: 22.2 (5.0) s⁻¹; CONs: 22.1 (2.6); p=0.92) or medullary R₂ (T1D: 33.9 (6.1) s⁻¹; CONs: 37.7 (4.6); p=0.14). Renal cortical perfusion was lower in T1D than in CONs (T1D: 163 (40) ml/100g/min; CONs: 224 (49) ml/100g/min; <0.01), but there was no difference in the medullary perfusion (T1D: 43 (11) ml/100g/min; CONs: 44 (15) ml/100g/min; p=0.92). Renal artery blood flow was lower in T1D than in CONs (T1D: 360 (130) ml/min; CONs: 430 (113) ml/min; p=0.01). A lower renal cortical perfusion was associated with a higher UACR (p<0.01) and with a lower renal cortical perfusion and artery blood flow were lower in persons with T1D and albuminuria than in healthy controls, confirming findings from previous studies. Impaired renal cortical perfusion and blood flow were associated with impaired renal function.

Funding: Private Foundation Support

PO0765

CKD-Associated Frailty Risk Trajectory over Time Among Patients with Newly Diagnosed Diabetes Mellitus: A Population-Based Cohort Analysis
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Background: Patients with chronic kidney disease (CKD) and diabetes mellitus (DM) are at high risk of frailty and adverse functional outcomes. CKD likely further aggravates the risk of frailty among patients with DM. However, whether the timing of CKD onset relative to incident DM affects the subsequent risk of frailty over time remains unclear.

Methods: We recruited patients with newly diagnosed DM but without frailty from a population-based cohort (n=488,458), dividing them into those without CKD throughout study period (7 years), with CKD prior to DM diagnosis, and with CKD years after incident DM. Their risk of frailty, based on a modified FRAIL scale, were examined. We used Cox proportional hazard regression to calculate CKD-associated risk of frailty, accounting for demographic, morbidities, medication, and prior hospitalization, followed by multiple regression analyses to calculate the annual probability of developing frailty starting immediately after DM occurrence.

Results: Among the enrolled patients with newly diagnosed DM, 80.8% (n=394,673) had no CKD throughout study period, while 3.3% (n=16,037) and 15.9% (n=77,748) had CKD prior to and after DM, respectively. Cox proportional hazard regression showed that newly diagnosed diabetic patients with CKD after DM had a significantly higher risk of developing frailty than those without CKD throughout study period (hazard ratio [HR] 1.649, 95% confidence interval [CI] 1.45 – 1.88), while those with CKD before DM had a higher but rather modest risk (HR 1.200, 95% CI 1.11 - 1.29). The annual probability of frailty occurrence was highest early during the course of DM and decreased slowly but gradually among CKD after DM group, while that of frailty remained stable throughout the study period among CKD prior to DM group (Figure).

Conclusions: The risk of CKD-related frailty exhibited temporal changes in patients with newly diagnosed DM. It would be prudent to carefully select the timing of providing frailty-oriented care in these patients.

PO0766

Understanding Patient Receptivity Towards Receipt of Prognostic Risk Score for Diabetic Kidney Disease
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Background: Few studies examined the attitudes of patients with diabetic kidney disease (DKD) on risk stratification tools. An intrinsic barrier to undertake a risk stratification test is knowledge, awareness, and desire to know the risk of kidney disease. This study aimed at exploring the baseline knowledge about kidney disease and type 2 diabetes mellitus (T2DM) as a major contributing factor, alongside possible motivators, and the patient’s receptivity towards risk score delivery of KidneyInteLex, a novel prognostic test that assesses the risk of kidney disease progression over the next 5 years in patients with DKD stages 1-3.

Methods: In May 2021, we contacted a subset of patients with stages 1-3 DKD and T2DM at one primary care site at the Mount Sinai Health System to communicate results obtained on their KidneyInteLex test and we administered a survey. We assessed patient knowledge about the test, their receptivity, and attitude on the usefulness of the test to improve their kidney health.

Results: A subset of patients (n=37) tested with KidneyInteLex in May 2021 were successfully contacted by the APRN on the DKD Care Navigation Team at Mount Sinai and completed the post-test survey. The majority of patients (70%) were aware diabetes is a contributing factor to kidney disease. 73% were unfamiliar with the prognostic test goals, while 27% were provided with an explanation by their physician. 89% were appreciative of the post-test call, and receiving risk scores through a post-test call were helpful for all patients (60% helpful, 40% very helpful) in improving their understanding of kidney health. Additionally, all patients were motivated to implement lifestyle changes to improve kidney health, and 63% desired educational content on diabetes, kidney disease and diet (Table).

Conclusions: Dedicated phone calls from the Care Navigation Team after KidneyInteLex testing enhanced patient understanding about kidney disease and revealed substantial motivation to take appropriate actions and receive further education for their kidney health.

Funding: Commercial Support - Renalytix, Clinical Revenue Support

Table: Patient Receptivity on KidneyInteLex Test Survey Questions Categorized by Predicted Themes

PO0767

Adequacy of Laboratory Monitoring of CKD for Diabetic Patients Empaneled with Primary Care
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Background: Studies have shown poor adherence to chronic kidney disease (CKD) guideline adherence in primary care, contributing to late referral to nephrology and suboptimal clinical outcomes. We sought to assess the performance of our health system in adhering to laboratory monitoring guidelines for diabetic patients with laboratory confirmed CKD.

Methods: We identified all adult patients empaneled in a regional health system who had creatinine and urinary albumin measurements between 2014-2016 excluding pregnant patients, as well as those transplanted or already on dialysis or hospice and crossed this cohort with our existing diabetic patient registry. CKD defined based on calculated GFR and CKD risk defined per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. We defined laboratory monitoring compliance as meeting the number of creatinine and urinary albumin measurements recommended by KDIGO per year with at least 3 months between measurement.

Results: 27943 diabetic patients had laboratory measurements allowing us to assess their CKD status. Of those 18466 (57%) had low risk/no CKD. Of those meeting CKD criteria, 13966 (50%) were missing a measure of albuminuria, 8030 (28.7%) had moderate, 3563 (12.8%) high and 2384 (8.5%) CKD risk. Compliance with laboratory monitoring was 82.7% for moderate risk, 59.9% for high risk and 44.8% of very high risk patients. Limitations include potential for access to disease monitoring outside of our health system.

Conclusions: Diabetic patients with CKD empaneled in our health system were often not adequately risk stratified for their CKD due to lack of attention to the need for albuminuria measures. For those who could be risk stratified, monitoring for low and moderate risk patients was adequate but the patients in the higher risk categories had worse guideline adherence. Better decision support systems are needed to improve kidney care for this high risk population.

Funding: NIDDK Support, Other NIH Support - NIA k23 AG051679
PO0768
Characteristics of Patients with CKD and Diabetes by Use of ACE Inhibitors or ARBs
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Background: The Center for Disease Research, Education and Hope (CURE-CKD) registry is curated from electronic health records (EHR) of >3.4 million patients with or at-risk of chronic kidney disease (CKD) at two, large healthcare systems. The study aim was to compare demographic and clinical characteristics of patients with CKD and diabetes (DM) by use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

Methods: Demographic and clinical characteristics of adults (≥20 years) with CKD and DM (guideline-based laboratory criteria, use of glucose-lowering agents, administrative codes) were described for the time periods of 2015-17 and 2018-20. Pearson’s chi-squared (categorical), Student’s t-test (normal, continuous), or Mann-Whitney U (non-normal, continuous) analyses determined differences between users and non-users of ACEI or ARB defined by prescriptions in the EHR.

Results: ACEI/ARBs were used in 59% and 58% of patients with CKD and DM in 2015-17 and 2018-20, respectively. Adults >60 years old, men, and White/LatinX individuals more commonly used ACEIs/ARBs (Table). In both time periods estimated glomerular filtration rate (eGFR) was significantly lower and systolic blood pressure was significantly higher in ACEI/ARB users versus non-users. The urine albumin-to-creatinine ratio did not differ by ACEI/ARB use. SGLT2 inhibitors and GLP-1 receptor agonists were more commonly used by ACEI/ARB users than non-users of these agents.

Conclusions: ACEI/ARB use remains sub-optimal in patients with CKD and DM and disparities in use exist by age, sex, and race/ethnicity. Use of glucose-lowering agents recommended for kidney and heart protection remains very low. Further studies are needed to elucidate reasons for under-use of recommended therapies in patients with CKD and DM.

Funding: Commercial Support - Bayer

PO0769
Impact of Non-Pharmacological Interventions in Indigenous Populations with Diabetes Mellitus on Cardiovascular and Kidney Disease: A Scoping Review Using the REAIM Framework
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Background: Diabetes mellitus is a common cause of mortality from cardiovascular (CV) and kidney disease. This scoping review utilized the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework to assess the impact of non-pharmacological interventions on CV and kidney health outcomes (KHO) in Indigenous populations.

Methods: We searched Medline, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO and other grey literature to identify studies that used non-pharmacological interventions (exercise, nutrition, self-management, health education, health worker, and cultural) to achieve improved glycaemic control, and reduction of clinical or laboratory markers of CV or KHO in Indigenous communities.

Results: Our search yielded 7,692 studies, from which 35 studies were selected. Culturally appropriate interventions were mostly utilized (77.1%); telehealth programs were least utilized (8.6%). Clinical and laboratory indices of CV and KHO were more frequently reported than those related to external validity: reach (60%), efficacy (52.1%), adoption (46.1%), implementation (41.9%), and maintenance (37.2%). (Table 1)

Conclusions: Due to the high prevalence of CV and kidney diseases in diabetic patients of Indigenous groups, studies using diabetes interventions need to report more items of external validity to allow the findings of such interventions to be translatable into practice.

Table 1

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<td>Reach</td>
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PO0770
Cause-Specific Death Differs Based on HbA1c Levels in Hemodialysis Patients with Diabetes
Soo-Young Yoon, Dae Kyu Kim, Jongho Lee, Shinseong Kang, Jin-sug Kim, Kyung Ilwon Jeong, Sangho Lee, Ju young Moon, Hyeon Seok Hwang, Kyung Hee University Medical Center, Seoul, Republic of Korea.

Background: Adequate glycemic control with achieving target HbA1c is critical in hemodialysis (HD) patients with diabetes and HbA1c level is closely associated with mortality risk. However, it is unclear whether different HbA1c levels affect mortality risk of cause-specific deaths or not.

Methods: A total 24,620 maintenance HD patients with diabetes were enrolled from the electronic health record-based registry data of Korean Society of Nephrology. Plasma HbA1c level was measured at the time of the study data entry, and patients were classified into six categories according to the HbA1c level (≤5.5%, 5.6-6.5%, 6.6-7.5%, 7.6-8.5%, 8.6%-9.5%, and >9.5%). In multivariable Cox regression analysis, we examined the relationship between HbA1c level and the risk of cause-specific death (cardiovascular, infection, non-cardiovascular/non-infection).

Results: Compared with the group with HbA1c 6.6-7.5%, the risk of all-cause mortality in each group tended to increase as HbA1c level rose; 0.99-fold (95% confidence interval [CI], 0.91-1.07) in HbA1c 5.6-6.5%, 1.08-fold (95% CI, 0.99-1.19) in HbA1c 7.6-8.5%, 95% CI, 0.99-1.19), 1.26-fold in HbA1c 8.6-9.5% (95% CI, 1.12-1.42), and 1.57-fold in HbA1c >9.5% (95% CI, 1.39-2.26). Non-cardiovascular mortality risk did not significantly increase across HbA1c strata except the risk in HbA1c >9.5% group (HR, 1.71; 95% CI, 1.29-2.26). Non-cardiovascular related/non-infection related mortality risk did not increase in all six HbA1c categories.

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>All-cause Mortality</th>
<th>Cardiovascular Mortality</th>
<th>Infection Mortality</th>
<th>Non-cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c 5.5-6.5%</td>
<td>0.99 (0.91-1.07)</td>
<td>0.99 (0.91-1.07)</td>
<td>1.00 (0.95-1.05)</td>
<td>0.99 (0.95-1.04)</td>
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<tr>
<td>HbA1c 6.6-7.5%</td>
<td>1.08 (1.01-1.16)</td>
<td>1.08 (1.01-1.16)</td>
<td>1.01 (0.97-1.06)</td>
<td>1.08 (1.04-1.13)</td>
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<tr>
<td>HbA1c 7.6-8.5%</td>
<td>1.26 (1.18-1.35)</td>
<td>1.26 (1.18-1.35)</td>
<td>1.03 (0.98-1.07)</td>
<td>1.26 (1.18-1.35)</td>
</tr>
<tr>
<td>HbA1c 8.6-9.5%</td>
<td>1.57 (1.30-1.91)</td>
<td>1.57 (1.30-1.91)</td>
<td>1.12 (1.03-1.21)</td>
<td>1.57 (1.30-1.91)</td>
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<tr>
<td>HbA1c &gt;9.5%</td>
<td>1.71 (1.29-2.26)</td>
<td>1.71 (1.29-2.26)</td>
<td>1.38 (1.20-1.59)</td>
<td>1.71 (1.29-2.26)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: All-cause mortality and cause-specific mortality risk were different according to HbA1c levels in the patients who were undergoing HD with diabetes. Furthermore, this study showed that cardiovascular mortality risk needs to be assessed in priority than infection or non-cardiovascular related/non-infection mortality risk when HbA1c level is increased in HD patients with diabetes.

PO0771
In-Hospital Outcomes in Diabetic Ketaosis and Impaired Kidney Function
Karthik Gangu, Aniesh Bobba. University of Missouri System, Columbia, MO.

Background: Diabetes Mellitus is one of the most common causes of End-Stage Renal Disease (ESRD) in the United States. In this study, we used the National Inpatient Sample (NIS) database to compare the outcomes of Diabetic Ketaosis (DKA) admitted in Chronic Kidney Disease (CKD) and ESRD to DKA with normal creatinine.

Methods: We performed a retrospective study by utilizing the 2016 NIS, which comprises 20% of hospital discharges for that year. We included patients aged 18 or older admitted to the hospital with a principal diagnosis of DKA. Diagnosis data were obtained by utilizing ICD 10 CM codes. A multivariate logistic regression model was used to analyze the effect of ESRD on mortality and intubation rate. Linear regression was used to analyze the impact of ESRD on length of stay. All outcomes were adjusted to age, sex, race, insurance status, Elixhauser Comorbidity index, hospital location, and characteristics.

Results: A total of 184,050 patients were included in the study, of which 12,605 had CKD and 6025 had ESRD. The mean age was 44.1 years (SD 12.8), and 51.9% of patients were female in ESRD. The mean length of stay was 5.2 days for the ESRD group and 3 days for DKA with the mean creatinine group. The adjusted length of stay was 0.5 days longer (p<0.001), and the adjusted cost of hospitalization was 13,684 US dollars more expensive in the ESRD group. Adjusted Odds Ratio for mortality 1.2 (CI 0.58-2.4, p = 0.61), and intubation 0.95 (CI 0.64-1.4, p = 0.81) were not statistically significant.

Conclusions: DKA in ESRD patients was associated with increased length of stay and cost of hospitalization. Further studies looking into factors contributing to the longer length of stay in the ESRD population will help in improving outcomes and significant cost reduction in taking care of these patients.

Table 1

*Adjusted for Age, sex, race, elixhauser comorbidity index, insurance status hospital location and characteristics.

PO0772
Hypoglycemia and Glycemic Status Ascertained by Continuous Glucose Monitoring vs. Blood Glucose in a Prospective Hemodialysis Cohort

Background: In non-CKD patients, evidence shows continuous glucose monitoring (CGM) provides convenient, automated, and less invasive measurements vs. conventional self-monitored blood glucose, and leads to reduced hypo-/hyperglycemia and glycemic variability (hypoglycemia risk factor), as well as increased time in goal glucose range and quality of life. However, accuracy of CGM interstitial glucose vs. gold-standard blood glucose measures has not been well-studied in dialysis patients.

Methods: In 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneous protoclated glucose measurements using 1) Dexcom G6 CGM devices vs. 2) blood glucose levels using capillary fingerstick or venous blood glucose, with the latter measured 4 times per day (before each meal and at night), plus every 30 minutes during HD. We examined the correlation of averaged CGM and blood glucose levels, and compared the prevalence of hypoglycemia detected by these methods.

Results: During the overall assessment period, Pearson and Spearman correlations for averaged CGM vs. blood glucose were 0.65 and 0.66; similar correlations were observed when stratified by HD vs. non-HD periods. A similar proportion of patients were identified as having American Diabetes Association (ADA) Level 1 Hypoglycemia (<70mg/dl) using CGM and blood glucose (33%). In contrast, a higher proportion of patients were identified as having ADA Level 2 Hypoglycemia (~54mg/dl) by CGM (33%) vs. blood glucose (11%). A similar proportion of patients were identified as having high glucose variability (%CV>36%) using CGM vs. blood glucose (11%).

Conclusions: In a prospective cohort of hospitalized HD patients with diabetes, CGM interstitial glucose via the Dexcom G6 remote access system showed similar correlation with blood glucose levels. Whereas CGM vs. blood glucose had similar detection of Level 1 Hypoglycemia, CGM had greater detection of Level 2 Hypoglycemia vs. conventional approaches.

Funding: Commercial Support - Dexcom, Inc.

PO0773
Effectiveness of Intradialytic Plantar Electrical Nerve Stimulation During Hemodialysis to Improve the Gait in Adults with Diabetes and Renal Failure: A Randomized Double-Blinded Controlled Trial
Abdullah I. Hamad,1 Ram kinker Mishra,2 Rania A. Ibrahim,3 Mincey Mathew,4 Mohamed Yahya Abdelhai Mohamed,1 Heba M. Ateya,1 Saifatullah Khan,2 Talal Talal,2 Bijan Najafi,4 Fadwa M. Al-Ali,3 Hamad Medical Corporation, Doha, Qatar;2 Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Houston, TX;3 Diabetic Foot and Wound Clinic, Hamad Medical Corporation, Doha, Qatar.

Background: Impaired mobility is a persistent problem among patients undergoing hemodialysis (HD). Although exercise could be beneficial, factors such as post-dialysis fatigue, time limitation, and severe frailty to travel may result in poor adherence to conventional exercise programs. To address this gap, we are exploring an alternative approach using intradialytic plantar electrical nerve stimulation (IPENS) provided during the routine hemodialysis process.

Methods: Participants were randomized into either an intervention group (IG: n=21, age=55±2.7 years, BMI=30.6±1.3 kg/m², female=31%) or a control group (CG: n=24, age=53.2±2.1 kg/m², female=41%). The IG received four IPENS during the routine HD process (3 sessions/week) for 12 weeks. The CG received an identical but non-functional device for the same period. Participants and therapy providers were blinded to the group allocation. Gait performance was assessed under single-task (ST) and dual-task (DT) conditions at the baseline, 6 week, and 12-week under supervised condition. To determine the effect of intervention, we estimated Cohen’s effect size d. In addition, time effect, group, and time x group effects were estimated using general linear model.

Results: All participants in the IG tolerated the IPENS and completed all therapy sessions, indicating the feasibility. While, under DT condition, cadence (steps/min) and stride time (sec) increased significantly in both groups over the time, we observed a trend towards higher improvement in IG group (Cohen’s d=0.34, p=0.086 for cadence and d=0.52, p=0.09 for stride time) with a medium effect size compared to CG. We observed significant time effect on other gait parameters under ST and DT conditions with the similar trends towards group effect.

Conclusions: This pilot trial provides earlier results on IPENS therapy’s feasibility and effectiveness as an alternative therapeutic program to improve gait in HD patients. Even though, the improvement didn’t reach statistical significance in our current sample size. However, the effect size was medium, which is very promising.

Funding: Government Support - Non-U.S.

PO0774
Economic Burden Associated with CKD Progression Based on Kidney Disease: Improving Global Outcomes (KDIGO) Risk Categories in Type 2 Diabetes
C. Daniel Mullins,1 Kevin Pantalone,2 Keith A. Betts,3 Jinlin Song,2 Yan Chen,2 Sheldon X. Kong,4 Rakesh Singh.5 University of Maryland Baltimore, Baltimore, MD;1 Department of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, OH;2 Analysis Group Inc, Los Angeles, CA;3 Bayer U.S. LLC, Whippany, NJ.

Background: CKD progression adds substantial economic burden in T2D. This study evaluated the medical costs associated with CKD progression defined by KDIGO risk categories in patients with T2D and CKD.

Methods: A prevalent cohort of adult patients with T2D and CKD who had measured using GFR and UACR indicating moderate or high KDIGO risk categories were identified from the Optum electronic health records database (Jan 2007–Dec 2019). CKD progression was defined as an increase in KDIGO risk category. Annualized costs for inpatient admissions, emergency room visits, and outpatient visits were evaluated for up to 2 years after the index date (i.e., the first record indicating CKD progression for progressed; the later of the first record indicating the patient’s risk category or two years before the end of follow-up for non-progressors).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Among 218,624 patients with baseline moderate risk, 41,986 (19%) progressed to high risk and 3,102 (1%) progressed to very high risk; among 50,461 patients with baseline high risk, 14,241 (28%) progressed to very high risk. Compared to non-progressors, the annual incremental costs were $5,193 for patients progressed from moderate risk to high risk, $18,168 for moderate risk to very high risk, and $15,280 for high risk to very high risk (Figure 1). Inpatient costs were the major driver of incremental costs. CKD-related medical costs contributed to 28%, 34%, 42%, and 44% of total medical costs in the 4 groups, highest in patients who progressed to very high risk.

Conclusions: Patients with T2D and CKD in KDIGO moderate or high risk categories had significantly higher medical costs when they progressed to a higher KDIGO risk category compared to those without progression. Preventing progression could bend the cost curve in patients with T2D and CKD.

Funding: Commercial Support - Bayer

PO0775

Geographic Variations in Healthcare Resource Utilization (HRU) and Costs and Their Associations with Albuminuria Testing in Patients with CKD and Type 2 Diabetes (T2D)

Rakesh Singh,1 Keith A. Betts,2 Jinlin Song,2 Yao Wang,2 Jay Elliott, Neil Warnock,1 Ryan Farej,1 Bayer U.S. LLC, Whippany, NJ; 2 Analysis Group Inc, Los Angeles, CA

Background: Albuminuria monitoring is critical for CKD management. The study evaluated the geographical urine albumin-to-creatinine ratio (UACR) monitoring patterns in the US along with the associated economic outcomes in patients with CKD and T2D.

Methods: Adult patients with T2D and CKD were identified from the Optum Clinformatics® claims data (Jan 2015-Dec 2019). HRU, healthcare costs (in 2020 USD), and percentage of patients receiving at least one UACR test were summarized by state during the one-year after T2D and CKD diagnoses. Patients who had dialysis or kidney transplantation before or during the study period were excluded.

Results: Among the 101,057 patients with T2D and CKD, the average annual healthcare costs were $28,636 and increased with CKD severity, from $20,122 (stage I, n = 4,070) to $38,072 (stage V, n = 242). Large variation exists across states ranging from $21,003 (HI) to $35,995 (IL) (Figure 1a). The average number of inpatient visits (range: 0.3 [AZ] to 0.7 [AR]), outpatient visits (18.3 [CO] to 29.8 [CT]), and emergency room visits (14.2 [OR] to 27.8 [CA]) varied substantially across states. States with lower UACR testing rates tended to have higher healthcare costs (Figure 1b).

Conclusions: Patients with CKD and T2D had high HRU and healthcare costs with large variations across states. Lower UACR testing rates were associated with higher economic burden.

Funding: Commercial Support - Bayer U.S. LLC

PO0776

Cardiovascular and CKD-Related Healthcare Costs for Patients with Type 2 Diabetes and CKD

Rakesh Singh,1 Jinlin Song,2 Elizabeth Faust,2 Xuyin Du,1 Sheldon X. Kong,1 Keith A. Betts,1 Bayer Corp, Whippany, NJ; 2 Analysis Group Inc, Los Angeles, CA; 3 Analysis Group Inc, New York, NY

Background: Cardiovascular (CV) events and chronic kidney disease (CKD) management incur high medical costs in patients with type 2 diabetes (T2D) and CKD. This study aimed to provide reliable regression-based cost estimates of these events among patients with T2D and CKD.

Methods: This study used Optum Clinformatics® claims data from 52,599 adults with T2D and CKD identified during 2015-2019 and followed until disenrollment, death, or end of data availability. Medical costs (2020 USD) associated with CV events and CKD management were estimated using a generalized estimating equation model adjusting for age, sex, as well as CV complications and medical costs at baseline. Costs were assessed in 4-month cycles as commonly evaluated in clinical trials in this population, with acute event costs assessed in the first 4 months after the incident CV events and renal replacement therapies (RRT). Mortality costs were assessed in the last month prior to death.

Results: The estimated 4-month CKD management costs were $7,725 for stage 1 or 2, $8,928 for stage 3, $10,809 for stage 4, and $11,879 for stage 5 (without RRT). The estimated acute event costs for dialysis and kidney transplantation were $87,538 and $124,271, respectively. The costs decreased to $49,573 and $7,079 in subsequent 4-month cycles following dialysis initiation and kidney transplantation. The estimated costs for acute CV events were $31,063 for heart failure, $21,087 for stroke, $21,016 for myocardial infarction, and $19,954 for atrial fibrillation ($30,500 with hospitalization and $5,162 without). In subsequent 4-month cycles, costs were $4,931 for heart failure, $2,327 for stroke, and $1,941 for myocardial infarction. The acute cost of hyperkalemia was $15,149 ($31,212 with hospitalization and $1,782 without). In the month before death, the costs associated with CV-related death, renal-related death, and death from other causes were $17,031, $12,605, and $9,900, respectively.

Conclusions: CV events and CKD management incur significant healthcare costs for patients with T2D and CKD. The cost estimates from this study may support the parametrization of economic models and help clinicians determine the cost-effectiveness of interventions.

Funding: Commercial Support - Bayer
Clinical and Histological Predictors of Renal Survival in Patients with Biopsy-Proven Diabetic Nephropathy

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The Sixth Hospital of Shanghai Affiliated to Shanghai Jiaotong University, Shanghai, China.

Background: Diabetic nephropathy (DN) is one of the most important complications of diabetes and has become the leading cause of end stage renal disease (ESRD). However, clinical and pathological factors alone can’t reliably predict renal survival in patients with biopsy-proven DN, potentially resulting in the delayed treatment of patients at a high risk of renal failure. Therefore, this study sought to develop and validate a predictive model incorporating both clinical and pathological markers to predict renal outcomes in patients with biopsy-proven DN.

Methods: A predictive nomogram was developed based upon data pertaining to 194 patients with biopsy-proven DN. The prognostic relevance of individual clinical-pathological variables was assessed through univariate and multivariate Cox regression analyses. A prognostic nomogram was then developed and validated based upon concordance (C)-index values, area under curve (AUC) and calibration curves. Internal validation was conducted through bootstrap resampling, while the clinical utility of this model was assessed via a decision curve analysis (DCA) approach.

Results: Nephrotic-range 24-hour proteinuria, late-stage chronic kidney disease (CKD stage 3-4), glomerular classification III-IV, and an IFNA score 2-3 were all identified as independent predictors of poor renal outcomes in DN patients and were incorporated into our final nomogram. Calibration curves revealed good agreement between predicted and actual 3- and 5-year renal survival in DN patients, while the C-index values for this nomogram was 0.845 (95% CI 0.826-0.864) and the 3- and 5-Year AUC were 0.933 (95% CI 0.898-0.968), 0.923 (95% CI 0.886-0.960). DCA analysis revealed that our nomogram was superior to models solely based upon clinical indicators.

Conclusions: A predictive nomogram incorporating clinical and pathological indicators was developed and validated for the prediction of renal survival outcomes in patients with biopsy-proven DN. This tool will be of value to clinicians, as it can serve as an easy-to-use and reliable tool for physicians to guide patient management based on individualized risk in order to improve patient outcomes.

PO0778

Histological Diabetic Nephropathy in Autopsied Diabetic Cases with Normoalbuminuria from a Japanese Community-Based Study: The Hisayama Study

Takuya Sasaki,1,2 Kaneyasu Nakagawa,3 Jun Hata,1,3 Yoichiro Hirakawa,1,3 Mao Shibata,1,4 Toshiaki Nakano,1 Nobuo Tsuibo,2 Yoshinoda Oda,3 Takenari Kitazono,1,4 Takashi Yokoo,2 Toshiharu Ninomiya.1,6 Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 2Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei School of Medicine, Tokyo, Japan; 3Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 4Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 5Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 6Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Background: Albuminuria is a clinical indicator of diabetic nephropathy (DN). However, it is controversial whether pathological DN lesions are present in diabetic individuals with normal albuminuria. We investigated the association between albuminuria levels and the frequency of DN lesions in autopsied diabetic cases from a Japanese community.

Methods: Autopsied specimens obtained from deceased people in the town of Hisayama from 2002 to 2017 were used in the present study. During this period, 131 deceased individuals with diabetes underwent autopsy examinations. A total of 106 autopsied cases with diabetes mellitus (mean age 76 years, 43.4% male) who died within 6 years since the last health examination were included in the study. Urinary albumin-to-creatinine ratio (UACR) levels were divided into three groups: <30.0, 30.0-299.9, and ≥300.0 mg/g. The kidney specimens were evaluated with light microscopy, and were categorized into class 0-1, IIa, IIb, and III glomerular DN lesions according to the Renal Pathology Society’s criteria. A Cochrane-Armitage test was used to examine the association between the UACR levels and the presence of class IIa or higher glomerular DN lesions.

Results: In the overall cases, the frequency of class IIa or higher glomerular DN lesions was 63.2% (IIa, 36.8%; IIb, 3.8%; and III, 22.6%). Its frequencies increased significantly with higher UACR levels (P for trend = 0.02, Figure). Even in individuals with UACR of <30 mg/g, the frequency of class IIa or higher glomerular DN lesions was 51.2%.

Conclusions: The present study showed a positive association of the UACR levels with the presence of class IIa or higher glomerular DN lesions, which were also frequently found even in the normoalbuminuric range, among autopsied diabetic cases from a Japanese community.

PO0779

Clinical and Pathological Significance of Orai1 Expression in Human Diabetic Nephropathy

Youjin Kwak, Hanwul Shin, Jun Young Lee, Jae seok Kim, Jae Won Yang, Seung-Kyu Cha, Minsoeb Eom. Yonsei University Wonju College of Medicine, Wonju, Republic of Korea.

Background: Diabetic nephropathy (DN) causes about half of ESRD. The attempts for targeted therapy for DN have been lacking to date. Store-operated Ca entry (SOCE) is a primary Ca influx mechanism in non-excitatory cells that is mediated by pore-forming subunit Orai1. Currently, it has been argued whether Orai1 overexpression protects against renal pathologies. Here, we investigated the significance of Orai1 expression in human DN.

Methods: Ninety-three DN patients from 2009 to 2019 were enrolled. The paraffin blocks were used to perform immunohistochemical staining for Orai1 (figure). Renal Pathology Society DN classification (RPS) and clinical parameters were compared with Orai1 expression. The results were compared by dividing them into a glomerulus (G) and tubulo-interstitium (T-I).

Results: In T-I, Orai1 was overexpressed in DN, and Orai1 expression was significantly correlated with the higher RPS and interstitial fibrosis & tubular atrophy score (p < 0.001). While Orai1 expression was correlated with serum Cr and CKD stages, eGFR and HbA1c were inversely associated with Orai1 expression (p < 0.001). By logistic regression, Orai1 expression was significantly correlated with the higher RPS and the advanced CKD stage. Moreover, Orai1 expression was strongly associated with the advanced CKD stage by the multivariate logistic regression (p = 0.002) (table). The result of G was similar to that of T-I.

Conclusions: It is suggested that Orai1 is a valuable biomarker for predicting the progression and prognosis of DN, that provides new perspectives on therapeutic targets for DN.

Funding: Government Support - Non-U.S.

The correlation between Orai1 expression and CKD stage in DN (Multivariate logistic regression)

<table>
<thead>
<tr>
<th>Adjusted OR (CI)</th>
<th>Parameter</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>ApoA, Sex, BMI, HbA1c, DN, on-treatment, HTN</td>
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<td>&lt;0.001</td>
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<td>Age (0-9)</td>
<td>2.896</td>
<td>&lt;0.001</td>
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<td>Orai1 (1-6)</td>
<td>2.961</td>
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</table>

BMI, body mass index; HTN, hypertension; G, glomerulus; T-I, tubulo-interstitium
PO0780

Prevalence and Risk Factors Associated with Diabetic Nephropathy in Patients with Diabetes Undergoing Nephrectomy
Laura Aponte Becerra,1,2 Juan D. Salcedo Betancourt,1,2 Alessia Fornoni,3 Oleksii Iakymenko,1 Gabriel Contreras,3 Sara Marin,3 Juanly N. Rodriguez,1,2 Noreen Mohsin,1 Oscar A. Garcia Valencia,1,2 Abraham Santana Rodriguez,1,2 Laura Barisoni,1 David B. Thomas,1 Jair Munoz Mendoza,1 University of Miami School of Medicine, Miami, FL; 2Jackson Memorial Hospital, Miami, FL; 3Duke University, Durham, NC; 4IYM Health Financial services, PLLC, Charlotte, NC; 5University of Miami Katz Family Division of Nephropathy and Hypertension, Miami, FL.

Background: Diabetic kidney disease (DKD) affects about 40% of patients with diabetes and is the most common cause of end-stage renal disease in the US. The prevalence of morphologic features of DKD, known as diabetic nephropathy (DN), is likely underestimated since kidney biopsies are performed when other diseases are clinically suspected. The availability of non-neoplastic kidney tissue from nephrectomies offers us the opportunity to evaluate the prevalence and risk factors associated with morphologic evidence of DKD.

Methods: A total of 198 nephrectomies of diabetic patients, where the status of the non-neoplastic kidney tissue was reported, were included. Clinical, demographic, and histological data were collected retrospectively. Logistic regression models were used to examine the association between clinical and demographic characteristics as primary exposure and morphologic evidence of DKD as the dependent variable.

Results: The mean age across all diabetic patients undergoing nephrectomy was 64±11 years, 59% were male, 9% African-American (AA), and 39% Hispanics. Clinical DKD was found in 47% of patients, 60% had hypertension, 66% had a GFR ≥ 60 mL/min/1.73m2 and 62% had no proteinuria. Morphologic features of DKD were observed in 56 (28%) patients. In multivariable-adjusted logistic regression analyses, the presence of morphologic features of DKD was significantly associated with older age (odds ratio [OR] per 10-year increase, 1.64 [95% confidence interval (CI), 1.08-2.48]), proteinuria (OR, 2.27 [95% CI, 0.99-5.17]), and neuropathy (OR, 4.92 [95% CI, 1.76-13.75]). The presence of morphologic features of DKD was associated with retinopathy only in univariate analysis (OR, 8.47 [95% CI, 1.65-43.47]). No association (p>0.05) was found with AA race, hypertension, clinical DKD, and eGFR was noted.

Conclusions: Morphologic features of DKD are highly prevalent in patients undergoing nephrectomy. Older age, proteinuria, and neuropathy were independently associated with significantly greater odds of morphologic evidence of DKD. Future studies should evaluate the prevalence of non-diabetic renal disease in patients with diabetes undergoing nephrectomy.

PO0781

Biopsy Results in a Diverse Diabetic Cohort
Douglas R. Farrell, Aparna Saha, Joti E. Tokita, Shuchita Sharma, Lili Chan, Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY.

Background: Diabetes is the most common cause of kidney failure in the US. However, many of these patients never receive a biopsy, and therefore diabetic nephropathy (DN) is presumed based on clinical features. Therefore, we sought to determine the prevalence and outcomes of non-diabetic renal disease (NDRD) in a diverse cohort of diabetic patients referred for biopsy.

Methods: Patients were included if they had a biopsy performed at the Mount Sinai Hospital from 2018-2019, and if they had a hemoglobin A1c > 6.5% or diabetes was mentioned in their past medical history. Charts were excluded if no data existed after biopsy, dialysis-dependence occurred prior to biopsy, and if insufficient amounts of glomeruli were observed. Baseline characteristics including age, gender, race/ethnicity, blood pressure, creatinine, and urine protein/creatinine ratio (UPCR) were recorded. Outcomes measured were 1 year UPCR, 1 year creatinine, need for dialysis, and death.

Results: In total, 81 charts were included for analysis, of which 21 biopsies had DN alone, 26 had DN + NDRD, and 27 had NDRD alone (Figure 1A). In patients with NDRD, a broad range of pathology was seen (Figure 1B). There were no significant differences in characteristics of patients with DN alone and any NDRD (Figure 1C). There was a non-statistically significant difference in median one year creatinine and one year UPCR between patients with DN and NDRD (1.67 vs. 3.07 (p=0.01) and 2490 vs. 3540 (p=0.23)). Additionally, there was a non-statistically significant difference in death and dialysis treatment between DN and NDRD patients, 4 (14%) vs. 3 (6%) (p=0.2) and 5 patients (18%) vs. 19 (36%) (p=0.09), respectively. DN had lower odds of requiring dialysis at 1 year from biopsy OR 0.39 (95% CI 0.13-1.19).

Conclusions: In our selected diverse population of diabetic patients with kidney biopsies, the majority of patients had NDRD on pathology. While not statistically significant, DN patients had lower follow up creatinine and UPCR, and less patients on dialysis at 1 year.
PO0783
Triglyceride-Glucose Index Is Associated with Renal Dysfunction in Stage 2 CKD Patients
Masami Araki. Sowa Central Hospital, Chino, Japan.
Background: SGLT2i, nephroprotective agent, are known to improve hyperinsulinemia and hyperlipidemia, especially triglyceride metabolism. However, their effects on renal function have not been clearly elucidated. Triglyceride-Glucose Index (TGI) has gathered attention as a new marker of metabolic syndrome. Since it reflects both lipotoxicity and glucotoxicity, we investigated the relationship between TGI and renal function.
Methods: In this single-institutional observational study, we screened subjects whose blood triglyceride, creatinine, and blood glucose) and body profile (abdominal circumference, height, and weight) assessment on the same day at annual health examinations between 2008 to 2018. Among these individuals, those with an estimated glomerular filtration rate (eGFR) value of 60–90 ml/min/1.73 m², which indicates stage 2 chronic kidney disease (CKD) in the first year, were included in the study. These were divided into two groups based on high and low mean TGI values during the course of the study. The changes in their renal function were compared. We evaluated both groups.
Results: Of the 19,940 individuals (73,084 tests) who were assessed initially, only 8,203 individuals had health data beyond one year. Among these, we examined 6,164 patients with stage 2 CKD (mean age: 49.2 ± 11.1 years, observation period: 1,906.1 ± 1,084.3 days, mean eGFR 75.5 ± 7.8 ml/min/1.73 m²). Univariate analysis by the Low-rank test showed that the renal function as significantly more deteriorated among individuals with a high TGI (P = 0.001). The difference remained significant after adjusting for gender, age, first-year eGFR, abdominal circumference, and follow-up systolic blood pressure using the propensity score matching method (p = 0.02).
Conclusions: In conclusion, among patients with mild renal dysfunction (stage 2 CKD), High TGI was associated with decreased renal function, and this did not change after adjusting for background factors.

PO0784
Effect of Dapagliflozin on Soluble Urokinase-Type Plasminogen Activator Receptor in Type 2 Diabetes with Albuminuria
Viktor Rotbain Curovic,1 Mie K. Eickhoff,1 Morten B. Houlind,2 Marie Frimodt-Moller,1 Tine Hansen,1 Jesper Eugen-Olsen,1 Peter Rossing,1,2 Frederik Persson,1 1Steno Diabetes Center Copenhagen, Gentofte, Denmark; 2Clinical Research Centre, Amager Hvidovre University Hospital, Hvidovre, Denmark; 3Københavns Universitet, København, Denmark.
Background: Given the documented protective effect of the sodium-glucose co-transporter 2 inhibitor, dapagliflozin on chronic kidney disease and the potency of soluble urokinase-type plasminogen activator receptor (sPAR) as a risk marker of the same, we investigated the effect of treatment with dapagliflozin on plasma sPAR in individuals with type 2 diabetes and albuminuria. Secondarily, we examined the association between the level of sPAR and the established early urinary proteomic classifier CKD273.
Methods: Post-hoc analysis of a double-blind, cross-over trial where persons with type 2 diabetes and albuminuria received treatment with dapagliflozin (30 mg/day) and placebo for 12 weeks in random order. The original primary outcome was change in the urinary proteomic classifier CKD273. sPAR level was assessed in plasma samples collected at all 3 visits. Effect of dapagliflozin on sPAR level was determined using unpaired t-test for comparison between baseline and end-of-treatment for the dapagliflozin and the placebo treatment period, and paired t-test for comparison between the two treatment periods. A secondary analysis investigated the association between baseline sPAR and CKD273 using Pearson correlation.
Results: Of the 36 persons who completed study, 11% were female, mean±SD age was 64±8 years, HbaA1c 73±15 mmol/mol (8.9±1.4%), eGFR 84±19 ml/min/1.73m², and median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329).
Conclusions: This post-hoc analysis could not demonstrate an effect of 12 weeks of treatment with dapagliflozin on plasma sPAR level in individuals with type 2 diabetes and albuminuria. In addition, plasma sPAR was not correlated to the urinary proteomic CKD273 classifier.

PO0785
Predictive Model of Non-Diabetic Nephropathy in Patients Affected by Diabetes
Sheila Bermejo,1 Irene Agraz, Andrez Vergara, Maria Jose Soler. on behalf of GLOSEN group Full d’Hebron Hospital Universitari, Barcelona, Spain.
Background: Between 50-60% of diabetics with renal involvement have non-diabetic nephropathy (NDN). Renal biopsy is critical for renal diagnosis that includes diabetic nephropathy (DN), NDN, or mixed form. The objective of the current study is to provide a tool in the daily clinical practice through a predictive model of NDN that is clue for the indication of renal biopsy.
Methods: Observational, retrospective and multicenter study of the pathological results of kidney biopsies in patients with diabetes from 2002 to 2014. A logistic regression analysis and the probability of presenting NND was calculated using a punctuation score. Results: The cohort of 832 patients includes 621 men (74.6%), median age 61.7±12.8 years, creatinine 2.8±2.2mg/dl and proteinuria 2.7 (1.2-5.4)g/dl. Time of evolution of diabetes was 10.8±6.8 years. 26.6%(n=221) of patients presented diabetic retinopathy, 18.8% (n=156) peripheral vasculopathy and 17.7% (n=147) ischemic heart disease. 288 patients (34.6%) presented microhematuria. 39.5% (n=329) presented DN, 49.6% (n=413) NDN and 10.8% (n=90) mixed forms. In the multivariate analysis, age (OR:3.03;1.01-8.18, p=0.002), absence of microhematuria (OR:0.6,0.4-0.86,p=0.005), absence of diabetic retinopathy (OR:3.97;2.7-5.82, p=0.001) and absence of peripheral vasculopathy (OR:1.61,1.03-2.52, p=0.038) were identified as independent risk factors for NDN. A ROC curve with an area under the curve of 0.724 was obtained. A predictive model obtaining a score (see figure) for each variable and finally a NDN prediction score was performed. In our new score, the number increases as increased the probability of NDN.
Conclusions: In our study, around 66% of biopsied patients with diabetes presented NDN. Microhematuria, absence of diabetic retinopathy, absence of peripheral vascular disease, and older age were identified as independent risk factors for NDN. We obtained a score that increases as increased the probability of NDN. This could be in a next future a useful tool for the clinical indication of renal biopsy in patients with diabetes and kidney disease.

PO0786
Metabolic Acidosis and the Risk of Progression to Diabetes in Patients with Prediabetes and CKD
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Background: Diabetes and metabolic acidosis are known risk factors for progression of CKD. Treatment of metabolic acidosis has been shown to reduce insulin resistance among patients with CKD and diabetes, but whether metabolic acidosis predicts progression from prediabetes to diabetes among patients with CKD is unknown.
Methods: Optum’s de-identified Integrated Claims-Clinical database of US patients (2001-2019) was queried for patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with ≥1 year prior data and ≥2 years of post-index data or death within 2 years. Patients with prediabetes (HbA1c 5.7 to <6.5%, fasting plasma glucose 100 to <126mg/dl, 175 g oral glucose challenge 140–199 mg/dl) were followed up for over 11.5 years for incident diabetes identified through lab values, diagnosis, or prescriptions. Cox proportional hazards models were used to evaluate metabolic acidosis as a predictor of incident diabetes, adjusting for age, sex, race, low-income status, geo-coded education and baseline BMI, eGFR, metabolic syndrome and polycystic ovary syndrome. Death was also evaluated as a competing risk.
Results: 7156/136,067 patients had evidence of prediabetes during the pre-index year. 47% (136/292) of patients with baseline metabolic acidosis and 46% (3143/6864) with normal serum bicarbonate developed diabetes during the outcome period (P=0.8).

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Underline represents presenting author.
Patients with metabolic acidosis developed diabetes sooner on average compared with normal serum bicarbonate (544 vs 643 days); however, baseline metabolic acidosis was not a significant predictor of time to incident diabetes in adjusted analyses (HR 1.20, 95% CI 0.96-1.49). Metabolic syndrome (HR 1.26, 95% CI 1.08-1.46), Black race (HR 1.28 [1.11-1.47]), male sex (HR 1.11 [1.01-1.21]), and higher BMI (HR 1.05 [1.02-1.08]) were associated with a higher risk of progression to diabetes. Higher baseline eGFR was associated with lower risk of progression to diabetes (HR 0.993 [0.988-0.997]).

**Conclusions:** In this longitudinal analysis of non-dialysis CKD stages 3-5 patients with prediabetes, metabolic acidosis was not associated with progression to diabetes.

**Funding:** Commercial Support - Tricida, Inc.

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**PO0788**

**The Gut Microbiome-Derived Phenyl Sulfate Is a Novel Predictive Marker and Cause of Albuminuria in Diabetic Kidney Disease**

**Koichi Kikuchi, Takaaki Abe, Tohokkai Daitu, Sendai, Japan.**

**Background:** Diabetic kidney disease (DKD) is one of the major causes of end-stage renal diseases (ESRD), and it is important to prevent from onset or progression of DKD. However, it is difficult to identify type 2 diabetes patients who are at risk of developing progressive DKD based only on measurements of glomerular filtration rate and albuminuria. Therefore, specific biomarkers are needed for a breakthrough in the good management of DKD.

**Methods:** Among 777 patients in a multi-center clinical study in diabetic nephropathy cohort (U-CARE), 362 patients with full data were selected. The plasma PS, PCS, IS, and TMAO level were measured by LC/MS/MS. The correlation between these level and various factors was calculated using the Spearman Rank-Order Correlation. Multiple regression analysis and a logistic regression analysis were used to identify the factors associated with PS, IS, PCS, TMAO, suPAR, uric acid or the development of 2-year ACR deterioration, respectively.

**Results:** As we previously reported (Kikuchi et al. Nat. Commun. 2019, ASN 2019), serum PS level significantly related with the basal albuminuria level in U-CARE study. In addition, logistic regression analysis showed among known ACR predictive factors, PS was the only factor which significantly related 2-year progression of albuminuria especially in patients with microalbuminuria. These data suggested that PS may have a potential as important as GS and IS in the pathogenesis of diabetic nephropathy. Therefore, we examined the relationship between albuminuria or renal function and IS, PCS, TMAO which were well-known as gut derived uremic solutes as well as PS. In addition, we examined the relationship between albuminuria or renal function and uric acid and were correlated with albuminuria. Among them, PS and uric acid were the factor which significantly correlated with the 2-year albuminuric-creatinine ratio (ACR) deterioration. Furthermore, we clarified that serum PS concentration level was high even in same patients who are preserved renal function (eGFR>60 ml/min/1.73m2), and high PS concentration patients were significantly increased 2-year ACR deterioration rate.

**Conclusions:** PS is predictive marker of albuminuria in the patients with microalbuminuria in DKD patients.

**Funding:** Commercial Support - Bayer US.  

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**PO0790**

**The Usefulness of Calcium/Magnesium Ratio in the Risk Stratification of Early Onset of Renal Replacement Therapy**

**Rita S. Alfonso, Ana Cabrita, Ana P. Silva. Centro Hospitalar do Algarve EPE, Faro, Portugal.**

**Background:** Recently, a growing number of studies have reported a close relationship between high serum calcium (Ca) and low serum magnesium (Mg) with vascular calcification. Endothelial dysfunction and vascular inflammation seem plausible risk factors for enhanced progression of kidney disease. The aim of this study is to evaluate the role of calcium/magnesium ratio as risk factor in CKD progression.

**Methods:** Observational, prospective study involving 693 patients (female=371) with stage 4/5 CKD. Patients were divided into two groups, according to the development of ESRD: G1 (n=541), who did not start renal replacement therapy (RRT) and G2 (n=152), who had started RRT. Several laboratory parameters were measured. Baseline characteristics were recorded and compared. Multivariate Cox regression analysis was used to identify independent factors associated with RRT initiation. A modified Poisson regression with robust error variance was used to estimate the cumulative relative risk for RRT initiation.

**Results:** The mean age was 70.09±12.51 years and eGFR was 19.9±8.11 ml/min. G2 had significantly lower serum levels of Hb (11.75±10.95 g/dl vs. 0.000), Ca (9.34±8.95 mg/dl vs. 0.000), Mg (1.92±1.40 mg/dl vs. 0.000), albumin (4.00±3.88 g/dl vs. 0.03) and cholesterol (183.17±172.39 mg/dl vs. 0.01), and higher serum levels of phosphorus (3.88±6.9 mg/dl vs. 0.000), Ca/Mg ratio (5.73±7.56 vs. 0.000) and PTH (209.71±338.84 mg/l vs. 0.000). In univariate Cox regression analysis, age, Hb, eGFR, Ca, Mg, phosphorus, Ca/Mg ratio and PTH correlated with onset of RRT, which were further tested using a multivariate COX regression. The results showed a significant correlation between high Ca/Mg ratio (Ca/Mg ≥ 6.00) and low serum magnesium (Mg < 1.24) and Ca/Mg ratio (HRa=1.292±0.002), and low levels of Mg (HRa=0.761±0.005) and eGFR (HRa=0.934±0.000) were independent risk factors to start RRT. Poisson regression showed that high Ca/Mg ratios (aPR=1.986; 95% CI 1.026-3.051; p=0.002), high levels of phosphorus (aPR=1.38±0.001), high levels of PTH (aPR=1.32±1.35±0.001) and low levels eGFR (aPR=0.927; 95% CI 0.891-0.964 vs. 0.000) were associated with a cumulative risk of RRT.

**Conclusions:** Our results suggest that the calcium/magnesium ratio is an independent predictive factor for the initiation of RRT. Further studies are required to validate the use of this novel marker as predictor of CKD progression.
Disparities in Quality of Care for Dialysis Patients
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Background: An understanding of disparities in quality of care for dialysis patients may inform priorities for quality improvement and approaches for achieving greater health equity. It is also not known whether disparities have been improving or worsening or whether they vary geographically.

Methods: We used Medicare claims and CROWNWeb data to evaluate disparities based on race, ethnicity, dual eligibility, and rural-urban location. Using criteria developed by AHRQ, we identified disparities in 2019 based on a statistically significant regression-adjusted difference in a quality indicator and at least a 10% relative difference between groups. We estimated generalized linear models with clustering for patients and adjustments for age, sex, cause of ESRD, duration of ESRD, and comorbid conditions at ESRD incidence. We examined national trends in disparities from 2015-20 and variation in disparity across the ESRD Network in 2019.

Results: There is evidence of disparities in U.S. dialysis patients for a range of quality indicators in 2019 (Table), some of which relate to measures in the ESRD Quality Incentive Program. Disparities involving racial minorities and dual eligible beneficiaries accounted for 13 of 16 measured disparities nationally. These disparities largely persisted over time and were found in most ESRD Networks.

Conclusions: There are ongoing racial, socioeconomic, and rural-urban disparities among dialysis patients in a range of quality indicators. There may be valuable opportunities for quality initiatives in ESRD to improve health equity.

Funding: Other U.S. Government Support

Real-World Clinical Performance Evaluation of the FX CorAL Dialyzer: A Retrospective Cohort Study
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Background: In-vitro dialyzer clearances as outlined in the Instructions for Use may not reflect clinical performance. Clinically, the in-vitro dialyzer performance varies between FX CorDiax, FX CorAL with slightly different in-vitro clearances.

Methods: 18 Hungarian and 33 Portuguese NephroCare Dialysis centers were randomly allocated to an implementation scheme. European Clinical Database data from 1,924 adult patients who switched from the FX CorDiax to the FX CorAL dialyzer between July 2020 and January 2021 were analyzed. To evaluate the clinical performance, we compared intra-individual changes of various parameters between 3 months before and 3 months after the dialyzer switch using paired t-test or Wilcoxon signed-rank test.

Results: The patients median age was 70 years, 64.2% were male, 38.4% had diabetes and 63.3% hypertension. The median dialysis vintage was 55.1 months. 88.6% of treatments were performed with online hemodiafiltration (HDF); 75.3% of patients had a fistula. After the dialyzer switch, the online clearance monitor Kt/V increased by 0.05 (2.7%). Among HDF patients, the effective infusion and convective volume increased by about 0.5 l and the effective treatment time increased by 4.2 min (1.8%). All mean changes were statistical significant (Table 1).

Conclusions: In this analysis of real-world FX CorAL dialyzer utilization, we observed statistically significant changes in performance parameters. In contrast to in-vitro results, our data suggest that the clinical performance of the FX CorAl and FX CorDiax dialyzer is comparable.

Funding: Commercial Support - Fresenius Medical Care

Table 1: Overall mean change after switch versus before switch

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean before (SD)</th>
<th>Mean after (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online Clearance monitor Kt/V</td>
<td>1.51 (0.26)</td>
<td>1.56 (0.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effective treatment time (min)</td>
<td>218.4 (23.7)</td>
<td>221.5 (24.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood flow (mL/min)</td>
<td>207.2 (56.8)</td>
<td>214.0 (54.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ultrafiltration (Kt/V)</td>
<td>25.0 (5.9)</td>
<td>25.0 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium and potassium</td>
<td>139.0 (3.6)</td>
<td>137.0 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein and urea transport</td>
<td>147.2 (18.5)</td>
<td>147.2 (18.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Risk Factors and Outcomes of Gout in Dialysis Patients: A Cohort Study of the United States Renal Data System (USRDS)
Anthony J. Bleyer,1 Yi Zhang,1 Onkar S. Kshirsagar,2 Brad Marder,2 Brian LaMoreaux,2 1Wake Forest University School of Medicine, Winston-Salem, NC; 2Horizon Therapeutics plc, Deerfield, IL; 3Medical Technology and Patterns Institute, Bethesda, MD.

Background: Limited research exists regarding gout among dialysis-dependent end-stage renal disease patients. This study aimed to evaluate the epidemiology, risk factors, and outcomes of dialysis patients with gout.

Methods: Using 2017 USRDS data, this study identified dialysis patients ≥18 years of age with Medicare as the primary payer. Baseline characteristics and comorbid conditions for dialysis-dependent patients with gout were assessed at dialysis initiation as well as 3-months preceding their gout diagnosis and compared with non-gout dialysis patients. All-cause hospitalization and mortality risk were also estimated and compared between gout and non-gout patients.

Results: Of 275,651 dialysis patients in 2017, 41,312 (15%) had ≥1 gout claims following initiation of chronic outpatient dialysis. More than 1/3 of gout diagnoses were made by internal and family medicine physicians. Compared to non-gout patients, gout patients were more likely to be older (mean 64.5 ± 56.8 yrs), male (62% vs 54%), of Asian race (6.2% vs 3.7%), and obese (31.4 ± 32.0 Kg/m²). Gout patients were also found to be more likely to undergo hemodialysis via central venous catheter (15% vs 13%). A higher comorbidity prevalence of comorbidities (67% vs 62%), hypertension (93% vs 74%), and cardiovascular conditions (heart failure [94% vs 30%], ischemic heart disease [49% vs 30%], peripheral vascular disease [32% vs 22%], stroke [12% vs 8%], acute myocardial infarction [7% vs 3%] and angina [4% vs 2%]). Adjusted regression analysis showed that older age (OR 2.11 for 45-64 vs ≤64 y, 95% CI 1.43-3.43), previous transplant (OR =2.37, 95% CI 1.24-2.50), and comorbid hypertension (OR =2.71, 95% CI 2.59-2.83) are the 3 most significant factors associated with gout diagnosis. In multivariate analysis, risk of hospitalization and mortality was higher by 11% (95% CI 13% and 9% (95% CI 12%), respectively in the year after diagnosis.

Conclusions: The prevalence of gout was 15% in the US Medicare dialysis-dependent population. Gout patients had a higher comorbidity burden especially for cardiovascular conditions and higher risk of hospitalization and mortality. Future studies are needed to elucidate whether improved recognition and management of gout may reduce the risk for worse cardiovascular outcomes.

Funding: Commercial Support - Horizon Therapeutics

Disparities in Staff CPR Performance Within US Dialysis Clinics: The Role of Clinic Resources and Patient Factors
Patrick C. Pan,1 Matthew Duphee,1 1Duke Clinical Research Institute, Durham, NC; 2Duke University School of Medicine, Durham, NC.

Background: Cardiac arrest occurs frequently in outpatient dialysis clinics, and implementation of a cardiac arrest response team improves patient outcomes. However, Black patients in dialysis clinics receive CPR from clinic staff less often compared to White patients. We examined the contribution of dialysis facility resources and patient factors to the observed racial disparity in CPR.

Methods: Retrospective cohort study linking the National Cardiac Arrest Registry to Enhance Survival (CARES) and Medicare Annual Dialysis Facility Report registries. We identified cardiac arrests occurring within US outpatient dialysis clinics via geolocation matching. Differences in facility size, quality, staffing and patient related factors were measured and compared according to patient race. Multilevel multivariable logistic regression models including these factors were constructed to examine the influence of these factors on the observed disparity in CPR rates between Black and White patients.

Funding: None

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277
Results: From 2013-2017, we identified 1,554 patients experiencing cardiac arrest in dialysis clinics. Compared to White patients, Black cardiac arrest patients diazyl in larger facilities (26 vs 21 dialysis stations, p<0.001), facilities with less RNs per station (0.29 vs 0.33, p<0.001), and facilities with lower quality scores (6.8 vs 6.3, p=0.04). Facilities treating Black patients cared for a higher proportion of patients with a history of cardiac arrest (41 vs 35%, p=0.001), HIV/Hepatitis B (5.1% vs 2.9%, p=0.001) and Medicaid enrolled patients (15% vs 11%, p<0.001). After accounting for these differences and other covariates, there was no change in the racial disparity for CPR in Black vs. White patients (OR=0.45 (95% CI 0.27-0.75). The disparity was greater among older Black patients compared to younger patients (interaction p=0.04). Other patient related and facility quality-related factors did not moderate the racial disparity in receipt of CPR.

Conclusions: The racial disparity in CPR delivery within dialysis clinics cannot be explained by differences in facility resources and quality. Reducing this disparity will require a multi-faceted approach including developing dialysis clinic-specific protocols for CPR and addressing potential implicit bias.

Funding: NIDDK Support

PO0795
Weekly Risks of Death and Hospitalization Among Incident Patients Undergoing Dialysis
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Background: During the first year of hemodialysis, risks of mortality and morbidity are elevated. However, it remains unclear when patients transition from relatively higher “incident” risk to relatively lower “prevalent” risk. We estimated trajectories of weekly risks of death and hospitalization among patients who recently initiated hemodialysis.

Methods: We analyzed data from the United States Renal Data System. The cohort included all patients who initiated outpatient hemodialysis in 2014-2017; for analysis of “incident” risk to relatively lower “prevalent” risk. We estimated trajectories of weekly risks of death and hospitalization during the first 52 weeks of hemodialysis. We used jointpoint regression with a maximum of five knots to estimate best linear interpolations of incidence trajectories.

Results: The cohort included 395,233 incident patients. Risk of death peaked in dialysis week 4. As displayed with jointpoint regression, there were four phases of risk: high and sharply increasing risk from week 1 to 3; high but steadily decreasing risk from week 3 to 13; moderate and gradually decreasing risk from week 13 to 30; and consistent risk from week 30 to 52. Risk of hospitalization was highest in dialysis week 1. There were four phases of risk: high but sharply decreasing risk from week 1 to 5; moderate and steadily decreasing risk from week 5 to 11; moderate and gradually decreasing risk from week 11 to 24; and consistent risk from week 24 to 52.

Conclusions: Weekly risks of death and hospitalization are highest during the first 13 to 14 weeks after initiation of outpatient hemodialysis, and gradually decline thereafter. However, risk trajectory details—including the timing of the transition from “incident” to “prevalent” status—vary among outcomes.

Funding: Commercial Support - AstraZeneca

PO0796
Shortened or Skipped Hemodialysis Sessions Attributed to Uremic Pruritus: A National Kidney Foundation Patient Survey
Johnson L. Gomez,1 Joseph A. Vassalotti,1,2 Gail Torres,3 Linda Singleton-Driscoll,1 Icahn School of Medicine at Mount Sinai, New York, NY; 2National Kidney Foundation, New York, NY; 3Chileve Consulting, Inc, Richmond, VA.

Background: Hemodialysis (HD) patients are at risk for uremic pruritus, a common and bothersome condition that may make it difficult for patients to complete the prescribed HD sessions. The purpose of this study is to investigate the extent to which pruritus contributes to patients shortening or skipping HD sessions. Studies have demonstrated that shortening and skipping HD treatments increases mortality risk.

Methods: An online survey of adults (18 years and older), across the U.S. from November 11-27, 2020, was conducted using two links posted on the National Kidney Foundation Facebook page. A $5 electronic Amazon gift card incentive was offered to the first 300 respondents with a valid email address.

Results: There were 692 participants among 2604 initial respondents, after excluding 1,252 for partial survey completion, 516 for not having kidney disease and 144 for kidney disease without HD treatment. Demographics and clinical characteristics include mean age 38.5 years ±11.8, 46.8% under 35 years, 45.5% females, 15% Black or African American, 9% Hispanic, 9% American Indian, 3% Asian, 74.7% employed or attending school, 45.3% with 1-5 years HD vintage, 81% treated with center HD and 19% treated with home HD. This population is younger and enriched for home HD and employment compared to 2018 results from the USRDS 2020 Annual Data Report, with only 11% HD age < 45 years, 2% treated with home HD and low employment prevalence. Pruritus was common with 64.0% (428/669) self-reporting itch that is at least somewhat intense on a Likert scale, including 25.7% (172/669) of patients reporting itching as very or extremely intense. Shortening or skipping an HD session because of pruritus was reported at least some of the time by 55.6% (334/601) and 50.4% (303/601) of participants, respectively. Patients reporting the itch as very or extremely intense were more likely to skip or miss HD treatments. Among the members of the HD care team, nephrologists 43.2% (299/692) were the most likely professional to be identified by patients to talk with about itchy skin.

Conclusions: This survey cohort of HD patients showed pruritus leading to skipped or shortened HD sessions occurred in about half of the patients. The results support uremic pruritus as a significant cause of skipped or shortened HD sessions for the dialysis care team to consider.

Funding: Commercial Support - Cara Therapeutics

PO0797
Association of Length of Interdialytic Interval and Patient-Reported Symptoms
Hsu Hsan Wen, Kinsuk Chauhan, Steven G. Coca, Girish N. Nadkarni, Lili Chan. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Symptoms burden of patients on in-center hemodialysis (HD) is high. Hospitalization and mortality is higher after the long interdialytic interval due to accumulation of fluid and electrolytes. It is unclear whether symptom burden is affected by the length of interdialytic interval.

Methods: We surveyed patients ≥18 years old, on HD for ≥30 days, and on HD three times a week at the Mount Sinai Kidney Center. Patients completed a survey about presence and severity (5 point scale) of 21 symptoms at the end of their HD treatments for 12 sessions. Symptom severity was calculated by multiplying the symptom with the severity and could range from 0 to 84, it was then summed per survey and the mean value per patient was calculated. We used negative binomial regression to determine the association of interval with symptom count.

Results: During the study period, 97 HD patients completed all surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The majority of patients reported symptoms, which ranged from a low of 8% for chest pain to 61% for fatigue (Figure 1A). More patients reported having symptoms associated with the long interdialytic interval than after the short interdialytic interval (5.8±0.5 vs. 4.7±0.5, P<0.001) (Figure 1B). Symptoms that tended to be more common after the interdialytic interval were fatigue, itching, dry mouth, bone pain, and restless legs (Figure 1C). After adjustment for age, gender, and race, the incidence rate of symptoms was 20% higher after the long interval (IRR 1.2, 95% CI 1.09-1.33).

Conclusions: Symptoms are common in patients on maintenance HD. Symptom burden is slightly higher after the long interdialytic interval than the short interdialytic interval.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

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Phosphate binders (PBs) are prescribed to control hyperphosphatemia among patients with chronic kidney disease. The need for phosphate intervention peaks will benefit from HD prescription modification. These patients reported 2,439,804 outpatient dialysis months in 2019. Among all patients, 28.4% did not report PB use in 2019 (26.4% among prevalent patients and 46.6% among incident patients). Among patients with any PB use, the average number of outpatient dialysis months was 10.9, of which 6.4 (60%) reported PB use. Average months with PB use differed by 3.8% for CAPD, 5.3 for CHPD, and 6.4 for hemodialysis.

Conclusions: We found gaps in PB use among patients receiving outpatient dialysis who were also prescribed a binder in 2019. Binder use was reported in 60% of all outpatient dialysis months for patients in our study, suggesting that PBs may have been underutilized or required only intermittently. Further studies are needed to determine the reasons for gaps in PB use and to identify opportunities for control of phosphate levels among patients with DD ESRD.

Funding: Commercial Support - Akebia Therapeutics, Inc.

Conclusions: There was a significant burden on quality of life and functional status. In the US hemodialysis (HD) and peritoneal dialysis (PD) population, there has been little reported on gout prevalence, patient characteristics, and associations with outcomes. We identified 233,564 patients with DD ESRD, of which 10% were incident. We identified incident and prevalent patients with DD ESRD in the 2018-2020 DOPPS cohorts and compared outcomes – including gout (vs. no gout) – among patients with vs. without a history of gout.

Results: Gout prevalence was 13% in HD and 21% in PD, and was highest among incident dialysis patients. Contributions of colchicine Rx (2-3%) and febuxostat Rx (1%) were lower than allopurinol Rx (9-12%), and additional contribution of gout diagnosis was minimal [Figure 1]. Both HD and PD patients with gout (vs. no gout) were older, more likely male, with higher BMI, and higher prevalence of cardiovascular comorbidities. After propensity score matching, mean ERI was 4% higher for gout vs. non-gout patients, while there was minimal evidence of association with clinical outcomes or PROs.

Conclusions: Gout was common in US HD and PD patients, with a large proportion of these patients treated with drugs indicated for hyperuricemia (allopurinol and febuxostat) and gout flares (colchicine). True prevalence was likely higher than observed when considering under-ascertainment of gout diagnosis history. This report provides a snapshot of gout in the US dialysis population and offers opportunities to expand on research to improve awareness and care for patients with gout and ESRD.

Funding: NIDDK Support, Other NIH Support - Agency for Healthcare Research and Quality (AHRQ), Commercial Support - This analysis was supported by Horizon. Other support includes: Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nissin Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torigi Fresenius Medical Care Renal Pharma Ltd.
PO0801

Fatigue Prevalence and Associations with Non-Diuretic Anti-Hypertensive Medications in the Maintenance Hemodialysis Population

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Background: It is well known that dialysis patients suffer from fatigue post dialysis. It is possible that fatigue is exacerbated by antihypertensive medications. We hypothesized that post-dialysis fatigue (PDF) duration was positively correlated with the number of antihypertensive medications.

Methods: We conducted cross sectional survey and 6 month retrospective medical record chart review at three privately owned dialysis clinics in Illinois. The survey consisted of 50 questions related to fluid and blood pressure management. The validated Post-Dialysis Fatigue and Time to Recover from Dialysis Survey (PDF TIRD), and the validated National Institute of Health Patient Reported Outcomes Measurement System fatigue short form. A random mixed effect model was created through a reverse stepwise process in order to assess associations. Chi-squared analysis was performed with categorical symptom data.

Results: One hundred and two patients consented to the study, 96 had complete medical records with all research variables and survey values captured. The average number of dialysis sessions per patient was 50.0 +/- 19. The average time on maintenance hemodialysis was 5.06 +/- 4.93 years with a range of 0.2 to 28 years. Seventy six percent (73/96) of dialysis patients suffered from post-dialysis fatigue. Most patients 53/96 reported that their fatigue was the worst after dialysis. On average patients required 462.67 +/- 655.18 minutes (7.7 +/- 10.92 hours) to recover after dialysis. In our random mixed effect model, the time required to recover post-dialysis was positively associated with the number of non-diuretic antihypertensive medications: For every anti-hypertensive medication, patients experienced an additional 210 minutes (3.5 hrs) of fatigue post dialysis fatigue.

Conclusions: Post-dialysis fatigue is a pervasive problem in the dialysis population that has significant consequences on patients’ quality of life. While fatigue has several important contributing factors, the number of non-diuretic blood pressure medications appears to exacerbate patient fatigue. Further investigation on the survival and quality of life benefits, including fatigue, of patients maintained on antihypertensive medications versus volume control strategies is needed.

PO0802

Dialysis Adequacy and Risk of Dementia in Elderly Hemodialysis Patients

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Background: Dementia is prevalent among elderly patients undergoing hemodialysis. However, the association between dialysis adequacy and the risk of dementia is uncertain.

Methods: A total of 10,567 patients aged >65 years undergoing maintenance hemodialysis who participated in a national hemodialysis quality assessment program were analyzed. We performed a propensity score method assigned to each hospitalization computed by multivariate logistic regression model to establish matched cohorts to reduce bias due to confounding covariates (age, gender, patients’ insurance type, quartile classification of median household income extrapolated from zip code, Elixhauser comorbidity index (ECI), hospital location and teaching status) between the 2 groups. We used survey logistic regression to evaluate the association of ADPKD with 30-day hospital readmissions.

Results: From 2016-2018, after propensity matching, there were 11,578 index admissions for ESKD patients with ADPKD and 11,422 index admissions for ESKD patients without ADPKD. Those who had ADPKD during index admissions had fewer 30 days readmissions (12.8% vs 15.3%, p<0.001). The cost of hospitalizations and readmissions in ESKD patients with ADPKD were higher than non-ADPKD patients (Figure 1A). Patients who were readmitted were more likely to have kidney transplant, non-routine discharges, and have non-elective index admissions. Longer length of stay, Medicaid insurance, discharge to short term hospital, specialized care, home health care and against medical advice were associated with increased odds of readmission, and higher ECI score and ADPKD was associated with decreased odds of readmission (OR 0.85, 95% CI: 0.76–0.96) (Figure 1B).

Conclusions: ESRD patients with ADPKD were less likely to have 30-day readmission than patients without ADPKD.

PO0803

Risk of 30-Day Hospital Readmission in Patients with ESKD with and Without Autosomal Dominant Polycystic Kidney Disease

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Background: Among end stage kidney disease (ESKD) patients with autosomal dominant polycystic kidney disease (ADPKD), relatively little is known about the epidemiology and risk factors for 30-day readmissions in the US. Therefore, we evaluated the 30-day unplanned readmission rates and predictors, and inpatient care costs among ESRD with and without ADPKD patients using a nationally representative, all-payer database.

Methods: We utilized the Nationwide Readmission Database from 2016-2018 to identify patients admitted for ESKD with and without ADPKD using ICD-10 codes. We developed a severity scoring method assigned to each hospitalization computed by multivariate logistic regression model to establish matched cohorts to reduce bias due to confounding covariates (age, gender, patients’ insurance type, quartile classification of median household income extrapolated from zip code, Elixhauser comorbidity index (ECI), hospital location and teaching status) between the 2 groups. We used survey logistic regression to evaluate the association of ADPKD with 30-day hospital readmissions.

Results: From 2016-2018, after propensity matching, there were 11,578 index admissions for ESKD patients with ADPKD and 11,422 index admissions for ESKD patients without ADPKD. Those who had ADPKD during index admissions had fewer 30 days readmissions (12.8% vs 15.3%, p<0.001). The cost of hospitalizations and readmissions in ESKD patients with ADPKD were higher than non-ADPKD patients (Figure 1A). Patients who were readmitted were more likely to have kidney transplant, non-routine discharges, and have non-elective index admissions. Longer length of stay, Medicaid insurance, discharge to short term hospital, specialized care, home health care and against medical advice were associated with increased odds of readmission, and higher ECI score and ADPKD was associated with decreased odds of readmission (OR 0.85, 95% CI: 0.76–0.96) (Figure 1B).

Conclusions: ESRD patients with ADPKD were less likely to have 30-day readmission than patients without ADPKD.

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280
**PO0805**

**Safety and Efficacy of Difenkafalin in Black or African American Patients on Hemodialysis with CKD-Associated Pruritus: Pooled Analysis of KALM-1 and KALM-2**

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**Background:** Difenkafalin (DFK) is an investigational, peripheral kappa-opioid receptor agonist that significantly reduced itch intensity in hemodialysis (HD) pts with CKD-associated pruritus (CKD-aP) in the Phase 3 KALM-1 and KALM-2 trials. People of Black or African American (AA) race were well represented in these studies. This pooled analysis reports efficacy and safety of DFK in Black or AA pts.

**Methods:** HD pts with moderate-to-severe CKD-aP were randomized to intravenous DFK 0.5 mcg/kg or placebo (PBO) 3 times/wk for 12 wks. The primary endpoint was the proportion of pts achieving a clinically meaningful 3-point improvement from baseline (BL) in the weekly mean of 24-hr daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores at wk 12. Secondary endpoints included proportion of pts achieving ≥3-point improvement from baseline in WI-NRS score and change in itch-related QoL score (5-D Itch and Skindex-10) from BL to wk 12. Adverse events (AE) through wk 12 were collected.

**Results:** Of 851 pts randomized in KALM-1 and KALM-2, 249 (29%) pts self-identified as Black or AA (DFK: 135; PBO: 114). Mean BL WI-NRS score was 7.2 and 7.3 in the DFK and PBO groups. A greater proportion of pts who received DFK vs PBO achieved clinically meaningful improvements in itch intensity and itch-related QoL. Most common treatment-emergent AEs (≥2%) with DFK occurring at a ≥1% higher incidence vs PBO were diarrhea (10.4% vs 6.2%), dizziness (10.4% vs 2.7%), vomiting (7.4% vs 4.9%), headache (5.2% vs 9.0%), and hyperkalemia (5.2% vs 2.7%). Serious AE incidence was similar between groups.

**Conclusions:** DFK significantly reduced pruritus intensity and improved itch-related QoL in Black or AA HD pts with moderate-to-severe CKD-aP. DFK was well tolerated with an acceptable safety profile. The safety and efficacy of DFK in Black or AA pts was similar to the overall population.

**Funding:** Commercial Support - Vifor Pharma

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**PO0806**

**Prevalence of Latent Tuberculosis Infection and Its Risk Factors in Japanese Hemodialysis Patients**

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**Background:** The majority of active tuberculosis (TB) cases develop from latent tuberculosis infection (LTBI). Since the risk of TB in hemodialysis (HD) patients is particularly high, interferon-gamma release assay (IGRA) for LTBI screening in HD patients is considered important. However, the prevalence and characteristics of LTBI in Japanese HD patients remain obscure.

**Methods:** We performed an observational cross-sectional study of LTBI using IGRA QFT-3G tests in 118 HD outpatients enrolled at 3 hospitals of varying location and function.

**Results:** Of the 118 patients, 96 were QFT negative, 7 were QFT indeterminate, 14 were QFT positive, and 1 was QFT judgment impossible. No patient had active TB. Confirmed (QFT positive) and possible (QFT positive/indeterminate) LTBI patients totaled 14 (11.9%) and 21 (17.8%), respectively. The LTBI possible group was significantly older and had a significantly higher rate of nephrosclerosis versus the QFT negative group. The indeterminate group had a significantly longer HD period. The QFT results were not remarkably affected by other clinical data, including hospital characteristics. The possible LTBI rate increased age dependently, with higher values from 60 years of age.

**Conclusions:** The prevalence of LTBI is high in Japanese HD patients, especially from the age of 60 years. Older age was a significant risk factor for LTBI, with prediction difficult using other clinical data. Extended HD may mask IGRA results. Therefore, aggressive screening for LTBI is advised in all HD patients regardless of hospital region or type, especially in patients over 60 years of age or newly commencing HD.

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**PO0807**

**Associations of Pre-Dialysis Care with Trajectories of Adverse Clinical Outcomes Among Patients Initiating Dialysis**

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**Background:** Health care during advanced chronic kidney disease likely influences outcomes during the first year of end stage kidney disease (ESKD). We assessed associations of nephrology care, erythropoiesis-stimulating agent (ESA) therapy, and red blood cell (RBC) transfusion before hemodialysis initiation with trajectories of adverse clinical outcomes during the first year after initiation.

**Methods:** We analyzed United States Renal Data System data. The cohort included patients who initiated outpatient dialysis in 2014-2017 and carried Medicare coverage during the year preceding dialysis initiation. We stratified the cohort by care in that one-year interval: nephrology care (per ESRD Medical Evidence Report), ESA therapy (per Medicare claims), and RBC transfusion (per Medicare claims). In each stratum, we estimated weekly incidence of all-cause death, hospitalization, and three-point major adverse cardiac events (MACE) during the first 52 weeks of dialysis. We used jointpoint regression to estimate incidence trajectories.

**Results:** The cohort included 132,879 patients. Before dialysis initiation, 65% received nephrology care, 14% used an ESA, and 32% received an RBC transfusion. As shown, nephrology care and ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. However, trajectories of weekly incidence during the first year were similar in all subgroups.

**Conclusions:** Pre-ESKD nephrology care and pre-ESKD ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. Regardless of pre-ESKD care, risks were higher during the early part of the first year.

**Funding:** Commercial Support - AstraZeneca

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PO0808

Temporary Changes in Hemodialysis Parameters in Patients Affected by COVID-19 Infection: A Visual Guide
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Background: ESKD patients on dialysis have been significantly affected by the COVID pandemic. By now, a substantial number of patients have survived the disease. We display graphically the temporary changes in dialysis parameters of patients that have survived COVID-19 infection.

Methods: All patients receiving hemodialysis at Emory dialysis centers diagnosed with COVID-19 infection between 3/1/20 to 1/31/21 who survived for at least 3 months were identified. The date of COVID-19 diagnosis was used to time-reference dialysis parameters including duration of hemodialysis, weight, ultrafiltration, mean arterial pressure pre-dialysis, hemoglobin, albumin, calcium, phosphorus, potassium, serum bicarbonate, absolute lymphocyte count and Kt/V. The temporary behavior of these parameters is presented graphically. Data manipulation, analysis and graphical display was performed using R-software and tidyscope package.

Results: 96 patients were identified. 82% were African-American with a median age of 64y/o. 52% were male and 60% were diabetics. The median time on dialysis was 2.5 years. All studied parameters showed a significant deviation from baseline measurements obtained in the 60 days prior to the diagnosis of COVID-19. The parameter with the least amount of change was Kt/V. In the subsequent 2 months after diagnosis, all of the parameters studied returned to baseline except for Potassium, that remained below pre-morbid levels 2 months after the COVID-19 diagnosis. These changes are presented in Figure 1.

Conclusions: COVID-19 infection has a significant impact on hemodialysis parameters as presented in figure 1. The temporary variation of the most common parameters associated with COVID-19 infection presented in this study can be used as reference for patients, dieticians, and nephrologists caring for ESKD affected by COVID-19.

PO0809

Reducing Haemodialysis Frequency in a Satellite Unit During the COVID-19 Pandemic
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Background: People dependent on unit HD are vulnerable to COVID-19. We describe the safety and outcomes of reducing HD frequency to minimise patient exposure to the virus.

Methods: HD was reduced from thrice to twice-weekly in selected patients for 9 weeks from March 2020. Urine output, heart failure, fluid-overload, hyperkalaemia, medication and patient preference were considered. Patients were asked to restrict dietary potassium, salt and fluid. Selected patients reducing HD frequency received 10g once-weekly sodium zirconium cyclosilicate (SZC). Group 1: Continue thrice-weekly HD Group 2: Twice-weekly HD +SZC Group 3: Twice-weekly HD -SZC. Pre-HD serum potassium (sK+) and bicarbonate (sHCO3-) were monitored. COVID-19 transmission, hospitalisation and death were recorded.

Results: Of 77 patients (mean age 70 years, 74% male), 17 continued three-weekly HD. 60 patients reduced to twice-weekly HD, of which 43 received SZC. There were 494 fewer HD treatments over 9 weeks. There was no significant difference in mean monthly sK+ in any group between March (pre-intervention), April and May; but 6 patients returned to thrice-weekly HD early due to hyperkalaemia or fluid-overload. SZC was increased to 10g twice-weekly in 15 patients. There was a reduction in mean monthly sHCO3- during twice-weekly HD. No changes were made to oral or HD bicarbonate prescriptions. There was no significant difference in pre-HD weight or SFB from baseline in patients dialysing twice-weekly. Only 2 of the 14 admissions over 9-weeks were related to hyperkalaemia or fluid-overload. 5 patients tested positive for COVID-19. 2 of the 3 deaths during this period were due to COVID-19. Both were elderly males with CVD and chronic respiratory disease. 1 patient died of a MI after returning home from HD. No deaths were attributed to a reduction in HD frequency. There was no evidence of COVID-19 transmission on the HD unit. No patients were transferred to the regional hub for HD due to COVID-19.

Conclusions: Reducing HD frequency in carefully selected patients is safe, and with strict infection control and timely COVID-19 testing, can reduce COVID-19 transmission and patient transfer to HD hubs. Dietetic review and SZC can reduce hyperkalaemia. Improved documentation of urinary output and cardiac function would optimise this approach.

PO0810

Paraoxonase 1 Gene Variants Concerning Spontaneous HCV Clearance in Hemodialysis Patients
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Background: We aim to explore associations between three PON1 SNVs (rs705379, rs854560, and rs662) and spontaneous clearance of HCV infection in uremic patients treated with maintenance HD. Epistatic interactions between tested PON1 SNVs and the IFNL4 variant rs368234815 were also investigated.

Methods: The study included 83 HD patients who spontaneously resolved HCV infection (all had known IFNL4 rs368234815 variant) and 104 subjects with persistently positive blood tests for HCV RNA (102 were successfully genotyped for IFNL4 rs368234815 variant). We genotyped PON1 by HRM method (rs662) or predesigned TaqMan SNV Genotyping Assay (rs854560, rs705379). We used a regression model including genetic and clinical data, which significantly differed patients with spontaneous HCV clearance and subjects with persistent HCV infection and could be
used as explanatory variables for HCV outcome. Epistatic interactions between tested PON1 SNVs and IFNL4 rs68234815 were analyzed by the multifactorial dimensionality reduction method.

**Results:** PON1 rs662 GG (OR 9.94, 95% CI 1.20 – 82.7, P = 0.022) and rs854560 TT (OR 4.31, 95% CI 1.62 – 11.5, P = 0.003) genotypes were associated with a higher probability for HCV resolution than the genotypes composed of at least one more frequent allele. The most common haplotype, rs662A, rs854560A, was inversely associated with spontaneous HCV clearance. Compared to this haplotype, the rs662G, rs854560T indicated a 5.09-fold (95% CI 0.99 – 26.2, P = 0.032) higher chance for HCV resolution. The first two haplotype epistatic gene-gene interactions PON1 rs662, PON1 rs854560, and IFNL4 rs68234815 (P = 0.094). Regression model, including the PON1 rs662 GG genotype, the IFNL4 rs68234815 TT/TT genotype, and chronic glomerulonephritis as possible predictive factors for spontaneous HCV clearance, showed that significant predictors of spontaneous HCV elimination were the IFNL4 rs68234815 TT/TT genotype (HR 2.84, 95% CI 1.43 – 5.62, P = 0.003) and RRT duration (HR 0.946, 95% CI 0.897 – 0.998, P = 0.042). The PON1 rs662 GG genotype provided P-value of 0.053.

**Conclusions:** The PON1 rs68234815 variant allele homozygotes are associated with a higher frequency of spontaneous HCV clearance in HD patients in univariate analyses.

PO0811

**Cost-Effectiveness of Hepatitis C Virus Testing Strategies in US Hemodialysis Centers**

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**Background:** The Centers for Disease Control and Prevention and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend screening all patients for hepatitis C virus (HCV) infection prior to starting outpatient hemodialysis (HD), every 6 months thereafter, and every 1-3 months if a center outbreak is detected. Yet, the cost-effectiveness of such screening frequency is not clear. We therefore sought to compare the clinical and cost-effectiveness of HCV testing strategies in US hemodialysis centers.

**Methods:** We parameterized the Hepatitis C Cost-Effectiveness (HEP-CE) model to reflect the US HD population, using United States Renal Data System and literature data. We simulated HCV infection, progression, treatment, and outbreaks within dialysis centers at the literature-reported frequency (approximately 1%). We competed 5 strategies to compare clinical outcomes and cost-effectiveness of screening, ranging from no testing to all, every 6-month HD testing, each with every 3-month screening during a simulated outbreak in 1% of centers. We estimated life expectancy, quality-adjusted life years (QALYs), total HCV infections identified and cured, liver-related deaths, costs (US$2019) and incremental cost-effectiveness ratios (ICERs). We simulated cohorts of 100 million individuals over a 20-year time horizon and assessed a health sector perspective.

**Results:** With no HCV testing or treatment, average life expectancy was 5.22 years, with 2.5 million HCV infections, 678,350 cirrhotic individuals, and 182,646 deaths from liver disease (Table 1). Screening only at HD initiation increased HCV care rates by 77% and decreased liver deaths by 79%, with an ICER of $71,533 per QALY saved compared to no screening. Increasing screening to every 2 years decreased liver-related deaths by an additional 51% with an ICER of $119,853 over screening at HD entry only. Screening annually or every 6 months was not cost-effective using a willingness to pay threshold of $150,000, even with halving baseline mortality rates or perfect linkage to care.

**Conclusions:** Testing for HCV in HD provides good economic value, but current CDC and KDIGO recommended intervals are not cost-effective.

**Funding:** NIDDK Support, Other NIH Support - NIDA, NIAID, Private Foundation Support

PO0812

**Disease Activity and Adverse Events in Patients with ANCA-Associated Vasculitis Undergoing Long-Term Dialysis: The DIAVAS Study**

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**Background:** Kidney impairment of ANCA-associated vasculitides can lead to kidney failure. Patients with kidney failure may suffer from vasculitis relapses, but are also at risk of infections and cardiovascular events, which questions the maintenance of immunosuppressive therapy.

**Methods:** Patients with ANCA-associated vasculitides initiating long-term dialysis between 2008-2012 in France, registered in the national REIN registry, and paired with the National Health System database, were included. We analyzed the proportion of patients in remission off-immunosuppression ever time, and overall and event-free survival on dialysis ( censoring for kidney transplantation). We compared the incidence of vasculitis relapses, serious infections, cardiovascular events and cancers before and after dialysis initiation.

**Results:** 229 patients were included: 142 with granulomatous polyangiitis (GPA) and 87 with microscopic polyangiitis (MPA). 82 patients received a kidney transplant. Mean follow-up after dialysis initiation was 4.6 ± 2.7 years. The proportion of patients in remission off-immunosuppression increased from 23% at dialysis initiation to 62% after 5 years. Overall survival rates on dialysis were 86%, 66% and 54% at 1, 3, and 5 years, respectively. Main causes of death were infections (35%) and cardiovascular events (26%), not vasculitis flares (6%). The incidence of vasculitis flares decreased from 111 to 7 episodes/100 person-year before and after dialysis initiation (p<0.05). Overall, during follow-up, 53% of patients experienced a serious infection, 52% a cardiovascular event, and 17% a vasculitis relapse.

**Conclusions:** The proportion of patients with ANCA-associated vasculitis in remission off-immunosuppression increases with time spent on dialysis. In this cohort, patients were far less likely to relapse from their vasculitis than to display serious infectious or cardiovascular events. Therefore, the benefit-risk balance of maintenance immunosuppressive therapies in patients on long-term dialysis should be carefully evaluated.

PO0813

**Analysis of Costs, Quality of Life, and Nutritional Status Between Patients with Two Different Models of Hemodialysis in Mexico: Chronic vs. Intermittent Hemodialysis**

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**Background:** In Mexico, access to conventional chronic hemodialysis (cHD) programs (two or three hemodialysis sessions a week) is only possible in a few patients. Intermittent hemodialysis (IHD) without social support usually are undergone during hemodialysis (IHD) sessions, this is weekly, biweekly or even monthly sessions when the signs and symptoms of dialysis urgency are present. We aim was to compare the costs, quality of life and nutritional status among different model hemodialysis: cHD versus IHD.

**Methods:** We performed a cost-utility study. Costs generated by HD sessions and indirect costs reported by the patient are evaluated to obtain out-of-pocket expenses (medicines, transportation, food, medical supplies). Nutritional status was evaluated through the malnutrition and inflammation score (MIS) and quality of life through the SF-36 questionnaire.

**Results:** Twenty patients were analyzed 55% male, with a mean age of 40.5 ± 14.9 years. The average cause of CKD was diabetes in 60%, and the main comorbidity was HTA (95%). Eleven in cHD and nine in IHD. In Fig 1, shown biochemical characteristics, MIS, grip strength, and costs are presented by study group. The quality of life analysis showed worse scores in symptoms; effects of kidney disease, morbidity of kidney disease; physical component; and mental component (p ≤ 0.05).

**Conclusions:** Although not statistically significant differences were identified in out-of-pocket spending between models, patients with IHD presented worse score MIS and quality of life. A health policy is necessary that allows universal access to renal replacement therapies in Mexico.

PO0814

**Potential Cost Savings Associated with the Reduction of Hospital Admissions by Using Online High Volume Hemodiafiltration (Hv-HDF) vs. High-Flux hemodialysis (Hf-HD)**

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**Background:** On-line HDF for maintenance dialysis patients is available in Europe and Canada but is essentially absent in the US. The National Institute for Health and Care Excellence (NICE) conducted a systematic review and built economic models to compare hemodiafiltration (HDF) with standard high-flux HD. They found HDF to be cost-effective due to benefits such as increased survival and reduced medication requirements. In addition, NICE found HDF using high convection volumes (~20+ L) to be beneficial in terms of higher QALYs gained at a lower cost. In this study, we evaluate the cost-effectiveness of using online HDF in the US.

**Methods:** Using a systematic literature search for clinical data, we validated the assumptions that 1) patients undergoing overnight HDF have higher survival rates and reduced medication requirements than patients who undergo standard Hf-HD, and 2) the incremental cost-effectiveness ratio(ICER) of overnight HDF vs. Hf-HD is $162,279/QALY gained, based on a recent publication by NICE. Two standard US hemodialysis programs (two or three dialysis sessions a week) are only possible in a few patients.

**Results:** 20 patients were analyzed 55% male, with a mean age of 40.5 ± 14.9 years. The average cause of CKD was diabetes in 60%, and the main comorbidity was HTA (95%). Eleven in cHD and nine in IHD. In Fig 1, shown biochemical characteristics, MIS, grip strength, and costs are presented by study group. The quality of life analysis showed worse scores in symptoms; effects of kidney disease, morbidity of kidney disease; physical component; and mental component (p ≤ 0.05).

**Conclusions:** Although not statistically significant differences were identified in out-of-pocket spending between models, patients with IHD presented worse score MIS and quality of life. A health policy is necessary that allows universal access to renal replacement therapies in Mexico.
the US may be difficult to apply within the US due to differing payment structures. This analysis estimates the potential cost-savings associated with reducing hospital admissions with online HvHDF (vs Hf-HD) based on published studies and USRDS cost data.

**Methods:** We updated the NICE systematic literature review on HDF studies, especially for articles on hospitalization by searching EMBASE (Ovid), PubMed and NIH EED from 2010 to present. We used an input-output Microsoft Excel® database to calculate the potential cost-saving of online HvHDF compared to Hf-HD from reducing hospitalization and estimating the savings associated with those averted hospitalization and missed in-center HD. The average cost of hospitalization was derived from USRDS and adjusted to 2021 ($17,181), and the average hospital stay was 6.42 days and assuming thrice weekly would result in 2.75 missed HD treatments. It is assumed that reimbursement rate for in-center HD is $253.13 per treatment and costs of treating with HvHDF and Hf-HD is equivalent.

**Results:** Out of 107 studies found, 4 reported hospitalization rates for HDF and Hf-HD, and 1 compared HvHDF with Hf-HD. This study found 10.8 fewer hospital admissions with HDF per 100 patient-years (Maduell, et al, High efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 33: 2019) and the average hospital stay was 6.42 days and assuming thrice weekly would result in 2.75 missed HD treatments. It is assumed that reimbursement rate for in-center HD is $253.13 per treatment and costs of treating with HvHDF and Hf-HD is equivalent.

**Conclusions:** The potential annual cost-savings of using HvHDF over Hf-HD in maintenance in-center HD was estimated at $1,931 PPPY or $193,671 per 100 patients.

**Funding:** Commercial Support - Fresenius Medical Care Renal Therapies Group, Waltham, MA

**PO0015**

**Predicting Decline in Residual Renal Urea Clearance via Random Forest Regression**

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**Background:** For incident hemodialysis patients, the decline of residual kidney function (KRU) over the first year of dialysis therapy is associated with adverse outcomes such as higher death risk. While several studies have identified biomarkers associated with higher risk of steeper KRU decline, we sought to employ more novel prediction utilizing a random forest regressor to identify important predictors of KRU after one year on hemodialysis.

**Methods:** We retrospectively reviewed a cohort of 5,141 patients who initiated in-center hemodialysis from 2007 to 2011 and had available KRU data at both baseline and during the 90 days after the one-year mark. 80% of the cohort was selected for the training dataset, with the remaining 20% used to test the model. Cross validation was utilized to minimize the number of trees and the mtry parameter. For feature selection, we used the 20 most important features from a random forest using all available predictors.

**Results:** In our cohort, mean age was 61 ± 14 years, with 66% men, 25% Black, 70% diabetes, and mean baseline albumin was 3.62 ± 0.42 g/dL. Median baseline KRU was 4.24 (6.39 — 2.69). Median KRU after one year was 1.74 (3.14-0.76). The random forest model yielded an overall mean squared error of 2.13 with noticeably stronger performance on the lower end of final KRU values. Using the median response as a classification threshold, the model achieved an AUC of 0.74. A variable importance analysis revealed that the model’s five most important predictors consist of baseline albumin, weight, post-treatment session, blood urea nitrogen level, and body mass index.

**Conclusions:** We showed that a random forest regressor can predict KRU values for hemodialysis patients after one year of treatment with moderately high accuracy. Utilizing our predictive models could aid patients and clinicians in determining the best course of treatment, which should be validated in future studies.

**PO0016**

**Predicting Time to Dialysis and Unplanned Dialysis Start Using Machine Learning Models**

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**Background:** Despite advances in nephrology care, a majority of patients are not well prepared for starting dialysis. This puts patients at a heightened risk of adverse outcomes such as increased hospitalization, higher health care costs and poorer quality of life. Most studies report prevalence of unplanned dialysis start between 40% and 60%. We have implemented a solution that allows the care team to combine their clinical judgement with the outputs of state-of-the-art machine learning models. These models learn patterns in historical data which lead to outcomes of interest.

**Methods:** We have developed and deployed a set of supervised machine learning models using gradient boosted decision trees that estimate the likelihood a patient with chronic kidney disease (CKD) requiring dialysis and having an unplanned start in the coming 18 months. Unplanned Dialysis Start (UDS) Model sits downstream of Time to Dialysis or Temporal Risk (TR) Model and scores the CKD patients who are predicted to need dialysis. We trained these models in the medical and pharmacy claims and lab data of 751,242 CKD patients spanning multiple years. Input features included demographics, medical history, social determinants of health, and medication adherence. We are using the model output for selection of beneficiaries in a kidney care management program. In addition, the care team is using the risk scores at the point of care.

**Results:** TR Model has AUC of 93% and F-score of 0.31 whereas UDS Model has AUC of 71% and F-score of 0.30. The models are relying on clinically relevant features in making their predictions. Top predictors include serum creatinine, serum albumin, serum phosphate, hemoglobin, CKD Stage, age, comorbidities, nephrologist visits, social determinants of health, and uremic symptoms. We are able to discover patients who are not receiving nephrology care but are at risk for an unplanned start.

**Conclusions:** Machine learning models developed in large claims and lab datasets can predict time to dialysis and risk of unplanned dialysis starts. These models can be integrated into care management programs to target high risk patients with interventions calibrated to the individual patient’s risk. An evaluation study is the next logical step.

**Funding:** Commercial Support - CVS Health
PO0818
Clinical Research Offers Potential Benefit to Patients and No Obvious Harm to Clinical Value
Vladimir Rigodon,1 Yue Jiao,4 John W. Larkin,1 Len A. Usvyat,4 Murilo H. Guedes,2 Thyago P. Moraes,2 Roberto Pecotis-Filho,3 Jeffrey L. Hynes,2 Robert J. Kossman,2 Michael S. Anger,5 Frank Wall,5 W. Maddux,5 Kurt Musiina,1 Frenova Renal Research, Waltham, MA; 3Fresenius Medical Care North America, Waltham, MA; 4Centre Hospitalier du Mans, Le Mans, France; 5Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 6Fresenius Medical Care, Global Medical Office, Waltham, MA.

Background: Randomized clinical trials (RCT) are underperformed in nephrology. This may be due to the uncertain impacts on quality measures. We assessed quality outcomes between research-conducting (RF) and research-naive (NF) dialysis facilities, as well as respective patient outcomes.

Methods: We used data from adult HD patients treated at national provider in the United States from 2017-2018. RF were 1:1 propensity score matched (PSM) to NF on patients/year, patient/facility exposure, % Medicare, % accountable care, region and quality outcomes were compared cross-sectionally. Research participants (RP) from facility analysis were 1:1 PSM to research naive participants (RNP) at baseline (research participation start or index date) on age, sex, race, Ethnicity, vintage, access, albumin, hemoglobin (hgb), congestive heart failure, ischemic heart disease, diabetes, missed treatments, and hospital day rates. Quality outcomes were compared longitudinally at 6 and 12 months.

Results: We found no differences in quality outcomes between RF and NF facilities. We observed RP had lower hospital day rates at 6 months after research participation start as compared to RNP, as well as higher % with albumin >=4g/dL at 6 and 12 months, higher % with iPTH 150-600 pg/mL within 12 months, and lower anemia target achievement (Figure 1).

Conclusions: We observed no significant differences in quality measures between facilities that conducted clinical trials vs those that did not. Participation in trials was associated with lower hospital day rates and better achievement of nutritional targets, but lower achievement of hemoglobin and transferrin saturation targets. Anemia results might be attributable to conservative hgb repletion in trials of new investigational drugs. Trial conduct appeared to do no harm to quality achievement and provide potential benefits to participants, which may be associated with additional evaluations/monitoring provided.

Funding: Commercial Support - Fresenius Medical Care North America

PO0819
Novel Insight About Pregnancy in Women on Chronic Dialysis: Systematic Review and Meta-Analysis Correlating Dialysis Regimen and Pregnancy Outcome
Emanuela Cataldo,1,4 Elisa Longhittano,2 Massimo Torreggiani,3 Antoine Chatrenet,1 Loreto Gesualdo,4 Giorgia B. Piccolii,3 Nephrology and Dialysis Unit,2 Fabio Perinei Hospital,3 Bari, Italy; 4Universita degli Studi di Messina Dipartimento di Medicina Clinica e Sperimentale, Messina, Italy; 5Centre Hospitalier du Mans, Le Mans, France; 6Azienda Ospedaliero-Antoine Emanuela Poggio, Le Mans, France; 7Fresenius Medical Care, Global Medical Office, Waltham, MA.

Background: Pregnancy in women on dialysis is an uncommon event, with a high rates of preterm delivery and neonatal death. Guidelines for management of dialysis in pregnancy are still lacking. Our aim is to identify dialysis regimens associated with best maternal-fetal outcomes.

Methods: Rapid systematic review. MEDLINE, EMBASE and COCHRANE library were searched (1950–2019: free terms on pregnancy and dialysis). Meta-analysis and metaregression were performed in case series dealing with the larger subset of maternal-fetal outcomes.

Results: The descriptive of 5204 pregnancies in 4746 HD patients, out of 52 case-series and registry data highlighted the importance of intensifying HD in pregnancy (5–6 sessions, >20 hours/week) to achieve a reduction in mortality and an increase in neonatal weight. The meta-analysis showed an increased risk of preterm delivery in women on chronic HD, decreasing with the increase in hours of HD and number of HD sessions. In addition, the meta regression demonstrated that increasing weekly hours of HD was associated to a lower risk of extreme preterm birth (<28 gestational weeks: p=0.016) and SGA (p=0.014) and with an increase in weight at birth (p<0.001). The same trend was observed for number of HD sessions. The high heterogeneity of data doesn’t allow disentangling the effect of the center of care.

Conclusions: Extend hours HD regimens in pregnancy improve maternal fetal outcomes. This improvement is linked both to HD rhythm and duration. The results obtained during pregnancy lead to reconsidering the concept of adequate HD at least in the young population.

Funding: Government Support - Non-U.S.

PO0820
Thrombocytopenia Predicts Mortality in Chinese Hemodialysis Patients: An Analysis of the China DOPPS
Xinju Zhao,1 Qingyu Niu,1 Liangying Gan,1 Fan Fan Hou,1 Xinling Liang,7 Zhao Hui Ni,6 Xiaonong Chen,4 Yuqing Chen,4 Keith McCullough,4 Bruce M. Robinson,4 Li Zuo,2 Peking University People’s Hospital, Beijing, China; 3Southern Medical University Nanshan Hospital, Guangzhou, China; Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China; 4Arbor Research Collaborative for Health, Ann Arbor, MI; 5Peking University First Hospital, Beijing, China; 6Ruijin Hospital AmMed Cancer Center Shanghai, Shanghai, China; 7Guangdong Provincial People’s Hospital, Guangzhou, China.

Background: Mortality rate was high in Hemodialysis (HD) patients. Our previous study suggested plateau counts might be a potential risk factor. However, few studies have examined the association of platelet count with mortality in HD patients. The aim is to examine if there is an association of thrombocytopenia (TP) with mortality and cardiovascular (CV) death in Chinese HD patients.

Methods: China DOPPS5 data was used. Fifty-eight of 1427 patients were excluded for missing platelet records. Demographic data, comorbidities, lab data, and death records were extracted. Participants were divided into 2 groups according to their platelet counts as TP group (platelet=100-10^9), and Non-TP group (platelet>10^9). The Non-TP could not be further divided into normal or above normal groups as limited by the sample size. Associations between platelet counts and all-cause and CV mortality were analyzed using Cox regression models. Stepwise multivariate logistic regression was used to identify related impact factors.

Results: Of 1369 patients, 201(14.7%) died and 102 (7.5%) died from CV disease. 11.2% (154) had TP at baseline. The mortality rates were 26.0% vs. 13.3% (p <0.01) in patients with and without TP. TP was associated with higher all-cause mortality after adjusted for covariates (HR:1.75, 95% CI: 1.12- 2.74), but was not associated with CV death after fully adjusted (HR: 1.75, 95% CI: 0.89, 3.45, Figure 1). Multivariate logistic regression showed that Urine output <200 ml/day, cerebrovascular disease, hepatitis B or C, and white blood cells were independent impact factors (P < 0.05).

Conclusions: Baseline TP's associated with higher risk of all-cause mortality in HD patients. Platelet counts may be used as early available outcome predictors among HD patients, though additional study is needed.

Funding: Government Support - Non-U.S.
Steady Exercise Improves Hand Grip and Leg Muscle Strength in Hemodialysis Patients

Ran-hui Cha, National Medical Center, Seoul, Seoul, Republic of Korea.

Background: Sarcopenia due to chronic inflammation and biochemical disturbances in chronic kidney disease is severe and more prevalent in patients on hemodialysis (HD). We longitudinally evaluated the hand grip (HGS) and leg muscle strength (LMS) in patients receiving HD and tried to find factors associated with muscle strength.

Methods: We screened (January 2020 (n=127)) and followed up (June 2020 (n=110) and December 2020 (n=104)) HGS (opposite the fistula side) and LMS (both sides) at single center by using digital hand and leg dynamometer (T.K.K.5401 and 5710c/5715, Takei scientific instruments Co. Ltd., Nigata, Japan).

Results: HGS and LMS showed good correlation (r = 0.658, p < 0.001). HGS (24.2 vs. 15.5 kg) and LMS (32.8 vs. 22.5 kg) were better in men (p < 0.001 and p < 0.001, respectively). Muscle strength was greater in men irrespective of age except for LMS in younger patients (< 60 years). Older patients (≥ 60 years) showed decreased LMS than others in women (p = 0.01). Patients who performed steady home- or hospital-based exercise showed marginally higher HGS (23.1 vs. 19.8 kg, p = 0.07) and significantly higher LMS (33.7 vs. 25.9 kg, p = 0.004). Steady exercise showed improvement of LMS throughout the study period (from January to June, p = 0.004, from January to December, p = 0.014). Multiple linear regression analysis proved male sex and steady exercise were factors associated with better HGS and LMS. Steady exercise showed greater impact on LMS in male patients with longer HD vintage (≥ 44 months) and on HGS in younger male patients with shorter HD vintage (< 44 months).

Conclusions: Sex, age, and steady exercise were important determinants of muscle strength in HD patients. And serum creatinine and dry weight, which reflects muscle mass, were also important in determining muscle strength. We need to encourage patients to do regular home- or group-exercise from the beginning of dialysis and introduce new feasible form of exercise for HD patients.

The Association Between Prevalence of Peritoneal Dialysis vs. Hemodialysis and Patients’ Home Distance to Dialysis-Providing Facilities

Paththarawin Paththaraimiting, Osama El Shamy, Kinsuk Chauhan, Aparna Saha, Hueil Hsuan Wen, Shuchita Sharma, Jaime Uribarri, Lili Chan. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Accessibility to dialysis facilities should play a role when deciding on a patient’s long-term dialysis modality. Studies investigating the effect of distance to nearest dialysis-providing unit on modality choice, however, have yielded conflicting results. We investigated the association between patients’ dialysis modality and the distances (driving and straight) to the closest HD and PD-providing units.

Methods: All ESKD patients (USRDS) who initiated in-center HD and PD in 2017, were 18-90 years old, and on dialysis for at least 30 days were included. Patients who resided in non-contiguous US or lived >90 miles from the nearest HD-providing unit were excluded.

Results: Among 102,247 included patients, median driving distance to the closest HD unit was greater for PD patients (3.9 vs 2.9 miles; p <0.001). Compared to HD patients, PD patients had longer driving distances to their nearest PD unit (4.4 vs 3.4 miles; p<0.001). PD utilization increased with increasing distance from patients’ homes to the nearest HD unit (OR 1.11, 95% CI 1.08-1.14 per 10-mile increase). This association did not change whether the PD unit was farther/closer than the nearest HD unit (Figure 1). This association was not seen when analysis was performed using straight line distance.

Conclusions: PD utilization increases with increasing driving distances from the nearest dialysis providing units (HD or PD). Using driving distance, but not straight line distance affects data analysis and outcomes. Increasing the number of PD units may have a limited impact on increasing PD utilization.
Change in Physical Activity and Function in Patients with Baseline Advanced Non-Dialysis CKD

Background: Progressive declines in physical activity and function are common in individuals with worsening chronic kidney disease (CKD). However, little is known about whether the transition to dialysis is associated with accelerated decline. We aimed to assess temporal rates of change in physical activity level and physical function in people with advanced CKD to determine whether the transition to dialysis was associated with accelerated decline.

Methods: Individuals with advanced CKD stages G4-G5 from the Canadian Frailty Observation and Interventions Trial (CanFIT) were included. Outcomes included change in physical activity level measured using the Physical Activity Scale for the Elderly (PASE) and physical function measured using the chair stand test, 4-meter gait speed, and grip strength. Unadjusted and adjusted generalized linear regression models were conducted to determine whether progression to dialysis was associated with greater decline in physical activity or physical function.

Results: Of 386 individuals, 162 individuals progressed to dialysis during the study period, whereas 224 did not. Both groups experienced statistically significant declines in self-reported physical activity, increased chair stand test times, and decreased gait speed. Compared to individuals with advanced nondialysis CKD, progression to dialysis was associated with greater increase in chair stand test time in unadjusted (beta estimate 6.05 seconds, 95% CI 2.36 – 9.74, p=0.001) and adjusted (beta estimate 5.23 seconds, 95% CI 0.75 – 9.71, p=0.02) models.

Conclusions: Although individuals with advanced CKD experience declines in physical activity and function over time, progression to dialysis is associated with accelerated decline in physical function as measured by the chair stand test. Future studies on interventions to delay or prevent declines associated with CKD progression and dialysis initiation are needed.

Validation of the Surprise Question in an Ethnically Diverse Population

Background: The “Surprise Question” (SQ) asks: “If you died in the next six months, would you be surprised?”—to estimate prognosis for dialysis patients has been largely limited to studies of older populations. We sought to evaluate the SQ as a clinical tool for predicting mortality in a large, real-world population of dialysis patients.

Methods: We recruited 10 dialysis centers (6 in NYC, 3 in Denver, CO, and 1 in Dallas, TX) with 1,507 patients. Dialysis staff screened patients monthly for 14 months (May 2019-June 2020) with the SQ to identify those who were SI and recorded outcomes including the number screened and number SI. In this rolling population of patients, we calculated the mortality risk per month of follow-up for SI and not SI and determined the annualized mortality risk was 41.9% for SI and 135 (50.2%) not SI. The annualized mortality risk was 41.9% for SI and 135 (50.2%) not SI. The annualized mortality risk was 41.9% for SI and 135 (50.2%) not SI.

Results: Of 386 individuals, 162 individuals progressed to dialysis during the study period, whereas 224 did not. Both groups experienced statistically significant declines in self-reported physical activity, increased chair stand test times, and decreased gait speed. Compared to individuals with advanced nondialysis CKD, progression to dialysis was associated with greater increase in chair stand test time in unadjusted (beta estimate 6.05 seconds, 95% CI 2.36 – 9.74, p=0.001) and adjusted (beta estimate 5.23 seconds, 95% CI 0.75 – 9.71, p=0.02) models.

Conclusions: Although individuals with advanced CKD experience declines in physical activity and function over time, progression to dialysis is associated with accelerated decline in physical function as measured by the chair stand test. Future studies on interventions to delay or prevent declines associated with CKD progression and dialysis initiation are needed.

Feasibility and Acceptability of Electronic Patient-Reported Outcome Measures (e-PROMs) Collection and Feedback in Hemodialysis Patients

Background: The “Symptom monitoring With Feedback Trial” (SWIFT) will assess whether 3-monthly symptom monitoring using the IPOS-Renal questionnaire with feedback to patients and clinicians with evidence-based symptom management recommendations, can improve health-related quality of life for adults on hemodialysis with kidney failure and improve adherence and health outcomes in these vulnerable patients.

Methods: We identified four themes: enabling efficient, systematic and multidisciplinary data collection into routine care, assistance to enhance uptake, clarity about e-PROMs purpose and utility of MI to address these obstacles. Verbatim transcripts and an iterative inductive/deductive approach were used to develop a hierarchical coding system. Two researchers independently identified and coded themes informed by social cognitive theory and the social ecological framework.

Results: See table below:

PO089
Perspectives on Motivational Strategies to Improve Hemodialysis Treatment Adherence in African Americans: A Qualitative Study

Background: Compared to White patients, African American (AA) patients have a four-fold higher prevalence of kidney failure and higher hemodialysis non-adherence. Adherence behaviors are influenced by psychosocial factors, including personal meaning and behavior, and self-confidence. It is not clear how these factors can be improved. We assessed perspectives of patients, family physicians and professionals on using motivational interviewing (MI), an evidence-based intervention to improve these psychosocial factors, hemodialysis adherence, and outcomes in AAs.

Methods: Self-identified AA hemodialysis patients (n=21), dialysis clinicians (MDs, NPs, FTE, CNWs and RDs) and health equity researchers (n=30) watched a brief video describing MI and then completed a semi-structured interview. Planned questions targeted unique barriers to hemodialysis adherence faced by AAs, and the perceived utility of MI to address these obstacles. Verbatim transcripts and an iterative inductive/deductive approach were used to develop a hierarchical coding system. Two researchers independently identified and coded themes informed by social cognitive theory and the social ecological framework.

Results: See table below:

Key Themes And Illustrative Quotes

<table>
<thead>
<tr>
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</thead>
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<td>&quot;I feel like I can talk to him more than I used to...&quot; (Clinician)</td>
</tr>
<tr>
<td>MI helps in understanding and addressing patient concerns</td>
<td>&quot;It’s not a lot of patient responsibility&quot; (MD)</td>
</tr>
<tr>
<td>MI helps in developing a shared treatment plan</td>
<td>&quot;Together, we’re like a team,&quot; (MD)</td>
</tr>
<tr>
<td>MI helps in assessing and addressing barriers to adherence</td>
<td>&quot;I’m thinking about my personal responsibility&quot; (Patient)</td>
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Funding: NIDDK Support

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Funding: NIDDK Support
and competing interests and barriers to PROMs data collection (physical limitations encompassing survey completion, low educational attainment and language limitations; fitting in with existing routines, and survey fatigue).

**Conclusions:** Clinicians and patients support the use of e-PROMs with feedback in HD. Clinician engagement and patient support, reliability of technology, timely symptom feedback, and interventions undertaken to address symptom burden are likely to improve acceptability and impact of symptom monitoring.

**Funding:** Private Foundation Support

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**PO0828**

Symptom Clusters in a Diverse Prospective Hemodialysis Cohort

Amy S. You,1 Sara S. Kalantar,

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**Background:** Hemodialysis (HD) patients experience a high symptom burden similar to that of patients with malignancy, which may adversely impact their quality of life and well-being. Given that emerging data in other fields (oncology) show that symptoms often occur in clusters, we examined the presence of symptom clusters in a diverse prospective HD cohort.

**Methods:** In 122 HD patients from the prospective Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study recruited across 16 outpatient dialysis clinics, the presence of CKD-associated symptoms was ascertained by the Dialysis Symptom Index (DSI), a 30-item validated survey that assesses symptom severity (score range, 0-40; higher score indicating greater severity), over 7/2020-8/2020. Using the DSI surveys, we examined the presence of symptom clusters (2 symptoms related to each other and occurring together) across domains categorized by organ system.

**Results:** The mean ±SD age of the cohort was 60 ±13 yrs, among whom 51% were female, 22% were Black, and 62% were Hispanic. Across the 30-item DSI survey, the most common individual symptoms included feeling tired/lack of energy (71%), dry skin (61%), itching (42%), muscle cramps (42%), and numbness/tingling in feet (41%). Upon examining co-existing symptoms, there was a high prevalence of symptom clusters, with the most common pairings including: 1) having trouble falling asleep + feeling tired/lack of energy or trouble staying asleep, 2) having trouble staying asleep + feeling tired/lack of energy or trouble staying asleep, 3) dry skin + itching, 4) dry skin + dry mouth, and 5) decreased interest in sex + difficulty becoming aroused.

**Conclusions:** We observed a high prevalence of symptom clusters in a well-defined, diverse prospective HD cohort. Further studies are needed to determine the physiologic underpinnings of concurrent symptoms in order to identify targeted therapies that can ameliorate the high symptom burden of HD patients.

**Funding:** NIDDK Support

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**PO0830**

Implementation and Effectiveness of a Supportive Care Learning Collaborative for Hemodialysis

Manjula Kurella Tamura,1,2 Margaret R. Stedman,1 Jialin Han,1 Steven M. Asch,2 Alvin H. Moss,3 Annette Aldous,2 Glenda Harbert,1 Amanda C. Nicklas,2 Dale Lupu,1 Laura Holdsworth,1 Stanford Medicine, Palo Alto, CA; VA Palo Alto Health Care System, Palo Alto, CA; West Virginia University Health Sciences, Morgantown, WV; Washington University Milken Institute of Public Health, Washington, DC; The George Washington University School of Nursing, Ashburn, VA; Stanford University, Stanford, CA.

**Background:** The objective of this study was to determine whether a learning collaborative for hemodialysis providers improved delivery of supportive care best practices.

**Methods:** Ten U.S. hemodialysis centers participated in a hybrid implementation-effectiveness pre-post study targeting seriously ill patients between April 2019 and September 2020. The collaborative educational bundle consisted of learning sessions, communication training and implementation support. The primary outcome was change in proportion of seriously ill patients with complete advance care planning (ACP) documentation. Healthcare utilization was a secondary outcome and implementation was assessed qualitatively.

**Results:** One center dropped out during the COVID-19 pandemic. Among the remaining nine centers, 22.9% (320/1395) of patients were identified as seriously ill in the pre-intervention period and 18.0% (226/1254) were identified in the post-intervention period. From the pre-intervention to post-intervention period, the proportion of patients with complete ACP documentation increased, and hospitalizations and emergency department visits decreased (Table). There was no difference in mortality, palliative dialysis, hospice referral or dialysis discontinuation. Screening for serious illness was widely and sustainably adopted. Goals of care discussions were adopted with variable integration and maintenance.

**Conclusions:** Supportive care best practices were feasible to implement in hemodialysis centers and largely sustained during the COVID-19 pandemic. We observed increased documentation of ACP and lower healthcare utilization after the intervention which could reflect a combination of collaborative and pandemic effects.

**Funding:** Private Foundation Support

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**Table. Advance care planning and health care utilization among seriously ill hemodialysis patients**

<table>
<thead>
<tr>
<th></th>
<th>Pre-implementation N = 258</th>
<th>Post-implementation N = 196</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmet goals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete ACP, N (%)</td>
<td>91 (35.6)</td>
<td>77 (40.1)</td>
<td>&lt;0.01</td>
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<tr>
<td>Any ACP, N (%)</td>
<td>(180/258)</td>
<td>(155/196)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Healthcare Utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative dialysis, N (%)</td>
<td>4 (1.6)</td>
<td>3 (1.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hospice referral, N (%)</td>
<td>22 (8.5)</td>
<td>20 (10.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Referral hospice, N (%)</td>
<td>3 (1.2)</td>
<td>5 (2.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>DSHSD referral, N (%)</td>
<td>3 (1.2)</td>
<td>4 (2.1)</td>
<td></td>
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</table>

**PO0829**

Implementing a Patient-Centric Educational Handout to Provide the Knowledge of Kidney Disease and Dialysis, Promote Self-Care, and Improve Quality of Life in Patients Starting Hemodialysis

Jennifer Griffiths, Kiran Shivaraj, Shrutir Kure, Michael D. Klein, Savnneek S. Chugh. Westchester Medical Center, Valhalla, NY.

**Background:** In the United States about 700,000 people need hemodialysis with most of them starting in the hospital. While patients on hemodialysis account for only 1% of Medicare beneficiaries, they account for 7% of total Medicare spending. While the cost of care is high among dialysis patient, the morbidity and mortality remain elevated with majority of deaths in the first 90 days of the start of dialysis. Studies has shown, lack of education in these patients about their treatments, dietary modification, fluid intake and vascular access. Early educational intervention of dialysis patient results in reduced re-hospitalizations and 90 days mortality in this vulnerable population

**Methods:** Extensive Pubmed search was performed to identify a validated clinical tool which will assess the pre-existing knowledge and post-interventional knowledge. Chronic Hemodialysis Knowledge Survey (CHEKS) was identified as a test and post-test questionnaire to assess the efficacy of the project. CHEKS was distributed to 10 new-start hemodialysis patients admitted at Westchester Medical Center. An evidence based educational handout was prepared and provided. Blood pressure, weight, and new-start hemodialysis patients. Educational material were given to read independently as well. As post-test was performed group of days later or at the time of discharge using the same CHEKS questionnaire. The mean and median pre-test and post-test scores were analyzed and efficacy of educational intervention was analyzed.

**Results:** The initial pre-test educational questionnaire on 10 patients showed a median score of 38.4% (5 out of 13 correct) and a mean score of 43.79%. The post-test score showed a median score of 92.3% (12 out of 13 correct) or a mean score of 90.9%. These results showed a 51.8% increase in educational score after the intervention was performed. Highest increase in patient’s knowledge were related to renal diet and fluid restrictions.

**Conclusions:** This study showed that the institution of structured educational activity can result in higher knowledge in dialysis patients, leads to better adherence to dialysis prescription and dietary recommendations. This along with limiting excessive fluid intake can result in reduce re-hospitalization and better self-care.

**Funding:** Private Foundation Support

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**PO0831**

Anxiety, Comorbid Depression, and Dialysis Symptom Burden

Daniel Cukor,1 Stephanie Donahue,1 Sri Lekha TummalaUppal,1,2 Andrew Bohmert,1 Jeffrey I. Silberzweig,1,2 Rognos Institute, New York, NY; 2Well Cornell Medicine, New York, NY, New York, NY.

**Background:** Anxiety is an understudied construct in patients with kidney failure. Its relationship to dialysis and its comorbidities, including symptom burden, is not well known. ‘Anxiety’ describes a category of diagnoses and it is unknown if its components of general worry, somatic anxiety, and anxiety sensitivity have differential relationships with outcomes. It is also not known if depressive affect moderates these relationships.

**Methods:** In this single center survey study, 100 participants completed an assessment of depressive affect (Patient Health Questionnaire-9, PHQ-9), worry (Generalized Anxiety Disorder-7, GAD-7), somatic anxiety (Beck Anxiety Inventory, BAI), anxiety sensitivity

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
(Anxiety Sensitivity Index, ASI), and dialysis symptom burden (Dialysis Symptom Index – DSI). Medical charts were abstracted for demographic information, number of missed dialysis sessions in the past 30 days (not rescheduled or due to hospitalization), and average interdialytic weight gain over the past 3 dialysis treatments. Results: The characteristics of the sample are found in the table below. People with elevated somatic anxiety (BAI > 15) had significantly higher rates of depression, worry, anxiety sensitivity, and dialysis symptom burden (p<.001, all cases). In a predictive model of symptom burden, age, race, and gender were not associated with symptom burden, and only somatic anxiety remained significant once adjusting for depression. In the final model, depression accounted for 40% of the variance and somatic anxiety accounted for an additional 37%. Conclusions: It appears that the impact on symptom burden of depression and worry/ anxiety sensitivity overlap significantly, but somatic anxiety, commonly found in panic disorder, may be a unique contributor to excess symptom burden.

Results: 19 patients completed KDQOL-36 at baseline and at 3 months; 15 also participated in an interview. Patients with high clinical levels of pain reported more overall symptom burden (p<0.001) and had significantly increased scores on all measured domains of the KDQOL-36 were observed from baseline to three months: “Symptoms” [mean difference (MD)=14.9, p<0.01]; “Effect” (MD=14.3, p<0.01); “Burden” (MD=7.3, p=0.04); “PCS” (MD=7.5, p<0.01); “MCS” (MD=7.2, p<0.04). These patterns of change are consistent with both incident and prevalent patients and across the different types of transitions. The qualitative interviews identified the following themes: 1) adapting to new circumstances (tackling change, accepting change), 2) adjusting together 3) trade offs, and 4) challenges of chronicity (the impact of dialysis, living with a complex disease, planning with uncertainty. Conclusions: The transition to a new or different type of dialysis is associated with improvements in HRQOL. In addition, qualitative data provided an in depth understanding of the transition experience, and revealed significant emotional and psychosocial processes that need to be considered during both incident and prevalent dialysis transitions.

PO0834
Prevalence and Demographic Correlates of Pain, Depression, Fatigue, and Readiness to Seek Treatment for These Symptoms in Hemodialysis Patients
Susan M. Devanar,1 Jonathan Yabes,1 Maria-Eleni Roumelioti,2 Jennifer L. Steel,1 Sarah J. Erickson,2 Mark L. Unruh,3 Manisha Jambh,4 1University of Pittsburgh Department of Medicine, Pittsburgh, PA; 2University of New Mexico School of Medicine, Albuquerque, NM.
Background: Patients with End Stage Renal Disease on hemodialysis (HD) experience a high burden of pain, fatigue and depressive symptoms. This study aims to better understand demographic differences in symptom burden and readiness to seek treatment among HD patients being recruited for an ongoing multi-center randomized controlled trial (TACare).
Methods: Patients in on-center HD were screened for clinical levels of pain (Likert scale ≥4), fatigue (Likert scale ≥3), and depression (Patient Health Questionnaire-9 score ≥10) within the last 2 weeks. Patients with at least one clinical symptom were then screened to assess readiness for seeking treatment for symptoms, and eligible to enroll if they were at least in the contemplation stage of Readiness for Behavior Change. Demographic differences in symptom screening and readiness to change (yes/no) were assessed through t-tests (age) and Chi-Square or Fisher’s Exact tests (race, ethnicity, gender). Symptom burden by readiness to change status was assessed using Chi-Square tests.
Results: Of the 390 patients who met eligibility criteria (mean age 59 years, 45% females, 15% Black, and 32% American Indian/Alaska Native, 29% Hispanic), 303 (78%) displayed at least one clinically significant symptom - pain, fatigue, or depression. Of these experiencing symptoms, 39% reported experiencing 1 clinically significant symptom, 35% reported 2, and 26% reported 3. There were no statistically significant differences by age, race, ethnicity, or gender in those reporting symptoms versus those who were not ready to seek treatment (80%) versus those not ready to seek treatment (20%). Of those who were experiencing symptoms, the percentage of patients willing to receive treatment increased as the number of symptoms increased (71%, 86% and 90% willing to receive treatment with 1, 2 or 3 symptoms respectively, p<.01).
Conclusions: The majority of HD patients report experiencing at least one clinically significant symptom and experiencing more of these symptoms increased readiness to seek treatment. Demographic difference in symptom burden and readiness for treatment were not evident in this sample and should continue to be the focus of additional research.
Funding: NIDDK Support

PO0835
Latino Patients’ Perspectives on Their Kidney Disease Education and Recommendations for Improvement: A Qualitative Study
Teresa K. Novick,1 Santiago Diaz,1 Kaydoo D. Choudhury,1 Doris A. Cubas,1 Francisco A. Barrios,1 Lilia Cervantes,1 Elizabeth A. Jacobs,2 1The University of Texas at Austin Dell Medical School, Austin, TX; 2University of Colorado, Denver, CO.
Background: In most states, Latinx immigrants with kidney failure receive dialysis in acute care settings on an emergency-only basis. What and how much kidney disease education they receive, and how to improve kidney disease education and outreach among Latinx populations is unknown. The objective of this study was to understand the kidney disease educational gaps of Latinx individuals who need but lack access to scheduled outpatient dialysis.
Methods: We conducted a qualitative, semi-structured interview study in a Texas hospital system from March 2020 to January 2021 with 15 individuals who received emergency-only dialysis when they were first diagnosed with kidney failure. We collected demographic information, and performed thematic analysis using the constant comparative method on interviews after they were audio-recorded, translated and transcribed verbatim.
Results: All 15 persons interviewed (60% male; mean age 51 years) identified as Hispanic, Mexican, andied knowing about their kidney disease more than 6 months before starting dialysis. The themes were: 1) lack of kidney disease awareness; 2) education provided was incomplete and poor quality; 3) lack of culturally concordant communication and care; 4) elements Latínx patients receiving emergency-only dialysis want in their education; 5) facilitators of patient activation and coping; and 6) Latínx patient recommendations to improve community outreach.

PO0832
Palliative and Conservative Care Consultation in Hemodialysis: A Survey
Karen Cohen,1 Geoffrey S. Techan.2 1Philadelphia College of Osteopathic Medicine, Philadelphia, PA; 2Lankenau Medical Center, Wynnewood, PA.
Background: Prior to initiating dialysis for patients with End Stage Renal Disease (ESRD), options other than dialysis such as conservative or palliative care are under-utilized. There may be a subset of patients who may not be ideal candidates for dialysis. Conservative kidney management can address the symptoms of kidney failure and can articulate goals of care with or without dialysis. Given the costs of healthcare, high morbidity and mortality in the ESRD population, we believe greater attention to conservative care prior to dialysis would result in patients having more comprehensive information prior to initiating dialysis.
Methods: Patients were surveyed at a large for-profit dialysis center in the suburban Philadelphia area in late December 2020. They were administered a 5 question survey about recalled experiences regarding referral patterns prior to dialysis. Potential responses were “yes,” “no,” or “do not recall.” Results: 37 patients were surveyed. Mean age was 63 years +/- 14, 70% were male, 95% were black. 24% of subjects reported discussing hospice and palliative care prior to dialysis initiation. 25% of patients >65 years old and 22% of patients <65 years old had such discussions. Chi square analysis was not statistically significant.
Conclusions: Only a small percentage of patients with ESRD on hemodialysis recall recommendations to improve community outreach. (6) Latinx patient recommendations to improve community outreach.

PO0833
Health-Related Quality of Life During Dialysis Modality Transitions: A Mixed-Methods Study
Chance S. Dumaing,1 Danielle E. Fox,2 Pietro Ravani,2 Maria Jose Santanta,2 Jennifer M. MacRae.2 1University of Saskatchewan, Saskatoon, SK, Canada; 2University of Calgary Cumming School of Medicine, Calgary, AB, Canada.
Background: Dialysis transitions may have an impact on health related quality of life (HRQOL), a patient defined priority for research and clinical care. We measured HRQOL and explored perceptions of adults who were initiating dialysis for the first time or transitioning to a new dialysis modality in a large urban centre in Canada.
Methods: In this prospective convergent parallel mixed-methods study we recruited eligible patients who were transitioning to dialysis from pre-care (n=9, incident) or undertaking a dialysis modality change (n=10, prevalent) between July and September 2017. Patients completed the five domains of the Kidney Disease Quality of Life (KDQOL-36) survey on their first day of dialysis treatment or first day of home dialysis training and underwent a semi-structured interview and follow up KDQOL-36 survey at 3 months.

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Conclusions: Latinx adults receiving emergency-only dialysis are usually unaware of their kidney disease until shortly before or after they start dialysis, and the education they receive is poor quality, and often not culturally tailored. Participants made feasible recommendations on how to improve education and outreach among Latinx communities.

Results: Of the 166 eligible patients, 101 consented to the study, and 97 completed all 12 surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The most common symptoms reported by the patients were fatigue (61%), cramping (59%), and dry skin (53%) (Figure 1). Nurses under-recognized 17/21 symptoms, mean relative difference of 34±33%. Physicians under recognized 16/21 symptoms, by a mean difference of 23±36%. Symptoms with the largest degree of under-recognition by nurses were dry skin (difference of 51 percentage points) and fatigue (difference of 42 percentage points). Physicians struggled most with recognition of cramping (difference of 39 percentage points) and fatigue (difference of 34 percentage points).

Conclusions: Patient symptoms were generally under-recognized by both dialysis nurses and physicians. While several symptoms such as shortness of breath, nausea, and vomiting were well recognized by nurses and physicians, nurses under-recognized dry skin and fatigue and physicians under-recognized cramping and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

PO0836
Improving Education and Satisfaction of Hemodialysis Patients Through Anonymous Feedback
Arun Rajasekaran, Anand Prakash, Spencer Hatch, Yan Lu, Abolfazl Zarjou.
The University of Alabama at Birmingham, Birmingham, AL.

Background: Patients on outpatient hemodialysis (OHD) are a particularly vulnerable population who may not feel comfortable sharing their experience given the complex and frequent nature of their care. This could lead to conceivable gaps in knowledge pertaining to improving their satisfaction and education. To account for this potential limiting factor and to build on previous surveys performed on OHD patients we conducted a study in nine of our university affiliated OHD units.

Methods: The study had 3 major objectives: 1) apprehend the level of satisfaction of patients with varying aspects of OHD related care, 2) evaluate level of understanding and education of patients regarding issues that pertain to their health and wellbeing, 3) identify potential avenues for improvement based on patients’ input. The survey was in English, paper based, with individual answer choices graded using a 1-5 rating scale [1:very poor, 2:poor, 3:neutral, 4:good, 5:excellent]. To ensure anonymity, the completed surveys were folded and dropped into a box.

Results: Among 516 screened patients 228 did not participate. Additional 35 patients were excluded for ≥ 1 reasons: legally blind, unable to read/write/speak English, advanced dementia, too frail. 253 eligible patients completed the survey. While the overall results were reassuring with 18 out of 24 questions yielding an average of ≥ 4.2 per question, we found specific areas for improving care and education. These included providing additional resources and information regarding palliative care, mental health, cardiovascular diseases, transplant process, addressing discomfort during OHD, improving privacy, and improving the time that the nephrologist spends with patients.

Conclusions: The US centers for Medicare and Medicaid services ESRD prospective payment system and quality incentive program requires that dialysis centers meet predefined criteria for quality of patient care to ensure future funding. We took advantage of an anonymous survey to further reflect on the potential needs of this patient population to enhance their quality of life and education. Despite specific limitations, our survey demonstrated patients undergoing OHD were overall satisfied and had a good understanding about their overall health. However, we identified several aspects to improve upon as requested by our respondents.

PO0838
Improving Food Insecurity in Patients with ESKD on Hemodialysis: Partnership with Local Food Bank
Elaine T. McCull, Emaad M. Abdel-Rahman. University of Virginia, Charlottesville, VA.

Background: Nutrition plays an important role in the management of ESKD on HD. Barriers to appropriate nutrition include medical, behavioral and socio-economic factors. Socio-economic factors may include poor purchase power and problems with transportation. Poverty rate at the area of University of Virginia (UVA) is 12.9%, which is 1.3 times the state average.

Methods: UVA partnered with the local food bank to meet the basic nutritional needs of our patients by delivering renal appropriate diet to patients at the dialysis unit, with an aim of reducing individual food insecurity.

Results: The current UVA food bank collaboration program distributes more than 50 bags each month and roughly 80% of the entire dialysis program has received at least one bag since the inception of the program. Presently 34 patients consistently received bags each month (bi-monthly or greater distribution of bags). There was no significant changes in weight, serum albumin, calcium, phosphorus or potassium between baseline and 6 months of consistently receiving food bags. 28/34 (82.4%) patients responded to a survey. Patients were 64.3% African American with 57.1% females with average age of 61.3 years. Average household of these patients were 2.2, receiving 2.3 bags/week with an average of 3.3 meals/week. While 50% of patients reported satisfaction with the program, 32.5% were very satisfied, 32.1% neutral and 3.6% were unsatisfied. 57.1% viewed the food as healthy, with 21.4% perceived food to be very healthy, 17.8% were neutral and 3.6% viewed the food to be unhealthy. The majority of the patients reported improved nutrition with these food items (82.1%). While only 10.7% of the patients reported they had to skip a meal because of being short on food, 85.7% reported that these bags helped them eat more meals on a regular basis.

Conclusions: Partnership with local food banks helps decrease food insecurity and improved satisfaction in patients on hemodialysis. Nutritional parameters did not improve, which may be due to consumption of supplemental food outside of the program. Expanding such programs to other dialysis units and to include fruits, vegetables, and meats could help decrease dependence on external sources of highly processed foods that contain high levels of potassium and phosphorus and may improve patients’ outcomes.

PO0839
Medication Burden and Prescribing Patterns Among ESKD Patients on Hemodialysis in the United States, 2013-2017
Julie M. Pauk, Min Zhuo, Seooyoung C. Kim, Rishi J. Desai. Brigham and Women’s Hospital, Boston, MA.

Background: The medication burden of patients with ESKD on HD is amongst the highest of any of the chronic diseases. This study describes the medication burden and prescribing patterns in a contemporary cohort of patients with ESKD on HD in the U.S.

Methods: We used the United States Renal Data System database from January 1, 2013 and December 31, 2017 to quantify the medication burden of patients on HD aged ≥18 years. We included patients who had continuous Medicare parts A, B, and D coverage with at least one Medicare part D prescription drug plan, were alive, and had complete medication data.

Results: Of the 166 eligible patients, 101 consented to the study, and 97 completed all 12 surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The most common symptoms reported by the patients were fatigue (61%), cramping (59%), and dry skin (53%) (Figure 1). Nurses under-recognized 17/21 symptoms, mean relative difference of 34±33%. Physicians under recognized 16/21 symptoms, by a mean difference of 23±36%. Symptoms with the largest degree of under-recognition by nurses were dry skin (difference of 51 percentage points) and fatigue (difference of 42 percentage points). Physicians struggled most with recognition of cramping (difference of 39 percentage points) and fatigue (difference of 34 percentage points).

Conclusions: Patient symptoms were generally under-recognized by both dialysis nurses and physicians. While several symptoms such as shortness of breath, nausea, and vomiting were well recognized by nurses and physicians, nurses under-recognized dry skin and fatigue and physicians under-recognized cramping and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

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for at least 3 months prior to January 1 of the respective year and excluded patients with a history of dementia or secondary diagnosis to this. Patients could contribute data to multiple yearly cohorts. We calculated the average number of prescription medications per patient during each respective year, number of medications within classes, including potentially harmful medications, and trends in the number of medications and classes over the study period.

**Results:** We included 163,228 to 176,133 patients from 2013 to 2017. In 2013, the mean age was 63.5 years and increased to 65.1 years by 2017. The percentage in the age 18-64 years category decreased (51.3% in 2013 compared with 45.9% in 2017) and the percentage in the older age categories all increased. In 2013, 51.8% were male and 48.2% were female, compared with 53.6% male and 46.4% female in 2017. The overall burden of medications decreased prescribed, from a mean of 7.4 (SD 3.8) in 2013 to 6.8 (SD 3.6) medications in 2017. Prescribing of potentially harmful medications decreased over time (74.0% with at least one harmful medication class in 2013 to 68.5% in 2017). In particular, the prescribing of non-benzodiazepine hypnotics, benzodiazepines, and opioids decreased from 2013 to 2017 (12.2% to 6.3%, 23.4% to 19.3%, and 60.0% to 53.4%, respectively). This trend was consistent across subgroups of age, sex, race, and low-income subsidy status.

**Conclusions:** Patients with ESKD on HD continued to have a high overall medication burden, with a slight reduction over time accompanied by a decrease in prescribing of several classes of harmful medications. Continued emphasis on assessment of appropriateness of high medication burden in patients with ESKD is needed to avoid exposure to potentially harmful or futile medications in this vulnerable patient population.

**PO0840**

The Impact of Late Initiation of Chronic Dialysis on Mortality: A National Longitudinal Study

George L. Worthen,1,2 David Clark,1,2 Keigir More,1,2 Amanda J. Vinson,1,2 Karthik K. Tennakone,1,2 Dalhouse University, Halifax, NS, Canada; ‘Nova Scotia Health Authority; Halifax, NS, Canada.

**Background:** Current Canadian guidelines recommend deferring dialysis initiation in asymptomatic patients until the glomerular filtration rate (GFR) reaches 6 mL/min/1.73m2, an “intent-to-defer” strategy. However, little is known about how dialysis initiation and post-dialysis outcomes are impacted when patients start at or below this threshold.

**Methods:** We sought to characterize the impact of starting dialysis at or below 6 mL/min/1.73m2 in a national retrospective cohort study of incident dialysis patients from 2004-2019. Dialysis data (excluding Manitoba and Quebec) was acquired from the Canadian Organ Replacement Register (CORR) and linked to hospitalization data using the well-established discharge abstract database (DAD). The cohort was restricted to only those who initiated dialysis as an outpatient and with previous nephrology follow-up of three months or more. Time to death was compared for those starting at or below 6 mL/min/1.73m2 (using the CKD-EPI formula) to those initiating between an eGFR of 6-15 mL/min/1.73m2 and analyzed using an adjusted cox proportional hazard model.

**Results:** A total of 63327 unique patients started dialysis from 2004-2019, of whom 39696 patients started dialysis as an outpatient after at least three months of nephrology follow-up. The mean age was 63.1/4, 68% were white, and 61% were male. 24% of the population started dialysis at an eGFR by CKD-EPI at or below 6 mL/min. Patients starting at 6 mL/min/1.73m2 or below were more likely to start dialysis with a CVC (59% vs 50%, p=0.001). During the study period 18979 patients died (48%). Starting dialysis at or below 6 mL/min/1.73m2 was associated with a longer time to death (HR 0.87; 95% CI 0.84-0.90) after adjusting for sex, race, age, dialysis access, diabetic kidney disease, and other comorbidities.

**Conclusions:** In this cohort of incident dialysis patients, those with an eGFR at or below 6 mL/min/1.73m2 had a lower risk for mortality compared with those starting with a higher eGFR. These findings support deferral of dialysis initiation beyond the threshold of 6 mL/min/1.73m2 in the absence of traditional indications.

**PO0841**

Hurricane Harvey Increased Need for Emergency Care in Patients with ESKD

Frederick I. Lemaitre1, Caroline M. Schafer2, Donald A. Molony1. Johns Hopkins Medicine, Baltimore, MD; 1The University of Texas Health Science Center at Houston, Houston, TX; 2The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.

**Background:** During natural disasters, end-stage kidney disease (ESKD) patients may represent a particularly vulnerable population due to interruption in care. We hypothesized that mortality and medical complications significantly increased in ESKD patients as a result of the disruptions in care related to Hurricane Harvey (HH).

**Methods:** Ten outcome variables for patients receiving outpatient, inpatient and home dialysis were evaluated at any time prior to the year of interest. Inclusion criteria were patients identified with ESKD by Medicare, had received at least one dialysis treatment within the observed timeframe, and had at least one year of follow-up before and four months before and/or four months after HH. All-cause mortality, patient admitted, admissions, emergency department (ED) visits, and diagnosis of complications.

**Results:** Using deidentified Medicare Claims data we identified 7,362 patients in the outpatient, 362 in the inpatient setting, and 810 in the home setting and compared outcomes in approximately stable populations in the years 2016 and 2018. Odds of ED visit was 31% greater (OR= 1.19, CI= [1.10, 1.29]) in 2017, compared to 2016 and 25% greater (OR= 1.25, CI= [1.14, 1.38]) compared to 2018. Odds of hyperkalemia was 37% greater in 2017 compared to 2016 and 15% greater in 2018 than 2016. Non-Hispanic black patients and men experienced lower odds of the outcomes of interest compared to white patients and women. Odds of gastrointestinal infection was 2.34 times more likely (OR = 2.33, CI = [1.32, 4.12]) in 2017 versus 2018. Black patients experienced increased odds of cerebrovascular accident (2.37 times more likely, CI = [1.20, 4.71]) in 2018 than in 2016. Non-Hispanic white women experienced increased odds of emergency department visit (1.42 times more likely, CI = [1.05, 1.95]) in 2017 than in 2016. Non-Hispanic white men experienced increased odds of emergency department visit (1.32 times more likely, CI = [1.00, 1.74]) in 2018 than in 2016.

**Conclusions:** Using Medicare claims data we found significant differences in Emergency Department (ED) visits and incidence of hyperkalemia in HH exposed patients compared to receiving outpatient dialysis in 2016 and 2018. Catastrophic events require special considerations for ESKD populations with increased risk of complications and burdens on the healthcare system. Better preparation for natural disasters may improve health outcomes associated with limited access to dialysis.

**Funding:** Private Foundation Support, Clinical Revenue Support

**PO0842**

Tuscany Network Program for Evaluation of Functional Status in Hemodialysis: The Rehabilitation in Hemodialysis Area Centro Tuscany (REACT) Study

Alessandro Capitanini, Fiammetta Ravaglia, Giuseppe L. Spatoliatore, Matteo Paci, Alessandro M. Pacini, Alberto Rosati. Nephrology and Dialysis Unit, USL Toscana Centro, Italy, Firenze, Italy.

**Background:** Frailty is associated with adverse outcomes among hemodialysis patients. The study session represents an opportunity to reassess functional status, to plan and monitor long-term physical exercise, leading to considerable improvement of quality of life and physical performance. The objective of our study is to assess the prevalence and predictors of frailty among a cohort of prevalent dialysis patients in our unit (RD ACT Study).

**Methods:** A regional program was designed to evaluate functional status in all patients performing hemodialysis in the 11 Dialysis Units of USL Toscana Centro. All patients are screened through the following tests: Short Form Health Survey (SF12); Elderly Falls Screening Test; Short Physical Performance Battery (SPPB); Handgrip test. Patients were assigned to three groups on the basis of the SPPB score: poor (SPPB < 5-6), moderate (SPPB 7-9) and good performers (SPPB >9).

**Results:** Of the 920 hemodialysis patients assessed for eligibility, 446 were enrolled and divided in 3 groups on the basis of SPPB score: Characteristics of the participants and functional status evaluation are shown in Table 1. SPPB score shows a significant correlation with handgrip of right arm (r = 0.48, p < 0.001), with handgrip of left arm (r = 0.21, p < 0.001), with Elderly Falls Screening Test (r = 0.48, p < 0.001), with SF12 physical component (r = 0.43, p < 0.001), with SF12 mental component (r = 0.46, p < 0.001). Principal predictors of SPPB score are Elderly Falls Screening Test (adjusted R² = 0.36), and age (cumulative adjusted R² = 0.71).

**Conclusions:** In our hemodialysis population, SPPB allowed identification of 3 frailty phenotypes. The information needed to determine patients’ degree of frailty can be gathered relatively easily, making frailty assessment a routine activity in hemodialysis patients’ evaluation.

Table 1

**PO0843**

Functional Prognosis Following Cerebral Hemorrhage in Patients on Hemodialysis

Yusuke Watanabe, Tsutomu Inoue, Hirokazu Okada. Sattama Ika Daigaku Igakubu Daigakuen Igaku Kenkyuka, Iruma-gun, Japan.

**Background:** It has been reported that patients on hemodialysis have a higher morbidity and mortality for hypertensive cerebral hemorrhage. However, little is known about the functional outcomes in the surviving patients.

**Methods:** We retrospectively analyzed 62 consecutive patients on hemodialysis who developed hypertensive cerebral hemorrhage between 2016 and 2020. Patient background data, data on the clinical presentation of cerebral hemorrhage, and details of the lifesaving brain surgery (craniotomy for removal of hematoma and ventricular drainage) were reviewed. The outcomes evaluated were in-hospital mortality and Glasgow Coma Scale (GCS), modified Rankin Scale (mRS), and Functional Independence Measure (FIM) scores at discharge.

**Results:** The median age of the patients was 66.5 years (interquartile range [IQR] 61, 72.5), and the median GCS score at admission was 13 (IQR 6, 14). Ventricular perforation was observed in 46.8% of patients. The median estimated hemotoma volume...
Carnitine is an important co-factor in long-chain fatty acid metabolism, and is involved in transport of long chain fatty acids into the mitochondria. Carnitine deficiency can present with hyperammonemia. We present a patient with ESRD with hyperammonemia and encephalopathy.

**Case Description:** This is a 48-year-old man with End Stage Renal disease due to nephrocalcinosis secondary to treatment complications due to X-Linked Hypophosphatemic rickets, presented to emergency room with nausea vomiting and severe confusion. He had a history of atherosclerotic disease disorder and was not on valproate or any other psychotropic medications. His liver enzymes were normal, ALT, albumin levels but he had persistently elevated alkaline phosphatase of 313 unit / L (40-130). PCO2 levels were normal, L. His ammonia level of 578 micro mol/L. There was no intracranial abnormalities imaging. Free carnitine (FC) levels came back as 26 nmol/ml (25-54), Acyl Carnitine (AC) 13 nmol/ml (5-30) AC/FC ratio of 0.5. Even though he had low normal FC levels, his AC/FC ratio was elevated and it has been proposed that car/acyl car ratio greater than 0.4 represents carnitine deficiency. Patient initiated on IV L carnitine 20 mg/Kg three times weekly without repeat episode of hyperammonia. It was also noted that patient no longer experienced intracranial hypotension.

**Discussion:** Carnitine deficiency causes accumulation of non-oxidized fatty acyl-coenzyme A in the mitochondria, which inhibits degradation of ammonia. This typically results in hyperammonemia, and clinicians should have high index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment is directed at replacement with intravenous Carnitine. Oral preparation index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment reduce the ammonia levels in valproate induced hyperammonemia.

**Conclusion:** In our single-center experience, a lower level of consciousness at admission associated with high mortality in patients on hemodialysis with cerebral hemorrhage. Survivors who underwent the lifesaving brain surgery had very poor functional outcomes at discharge.

**PO0844**

Hyperammonemia in an ESRD Patient

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**Introduction:** Carnitine is an important co-factor in long-chain fatty acid metabolism, and is involved in transport of long chain fatty acids into the mitochondria. Carnitine deficiency can present with hyperammonemia. We present a patient with ESRD with hyperammonemia and encephalopathy.

**Case Description:** This is a 48-year-old man with End Stage Renal disease due to nephrocalcinosis secondary to treatment complications due to X-Linked Hypophosphatemic rickets, presented to emergency room with nausea vomiting and severe confusion. He had a history of atherosclerotic disease disorder and was not on valproate or any other psychotropic medications. His liver enzymes were normal, ALT, albumin levels but he had persistently elevated alkaline phosphatase of 313 unit / L (40-130). PCO2 levels were normal, L. His ammonia level of 578 micro mol/L. There was no intracranial abnormalities imaging. Free carnitine (FC) levels came back as 26 nmol/ml (25-54), Acyl Carnitine (AC) 13 nmol/ml (5-30) AC/FC ratio of 0.5. Even though he had low normal FC levels, his AC/FC ratio was elevated and it has been proposed that car/acyl car ratio greater than 0.4 represents carnitine deficiency. Patient initiated on IV L carnitine 20 mg/Kg three times weekly without repeat episode of hyperammonia. It was also noted that patient no longer experienced intracranial hypotension.

**Discussion:** Carnitine deficiency causes accumulation of non-oxidized fatty acyl-coenzyme A in the mitochondria, which inhibits degradation of ammonia. This typically results in hyperammonemia, and clinicians should have high index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment is directed at replacement with intravenous Carnitine. Oral preparation index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment reduce the ammonia levels in valproate induced hyperammonemia.

**Conclusion:** In our single-center experience, a lower level of consciousness at admission associated with high mortality in patients on hemodialysis with cerebral hemorrhage. Survivors who underwent the lifesaving brain surgery had very poor functional outcomes at discharge.

**PO0845**

Neurocognitive Function with Convventional Hemodialysis vs. Post-Dilution Hemofiltration as Initial Treatment: A Randomized Controlled Trial (The DA-VINCI Study)

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**Background:** The ideal modality choice and dialysis prescription during the first renal replacement therapy (RRT) session remains controversial. We conducted a pilot study to determine the safety risk for hemodialysis versus hemofiltration and its relationship with neurocognitive assessment.

**Methods:** Twenty-four incident RRT patients were included. Patients were randomized to the conventional HD group or the post-dilution HF group. MMSE and MOCA tests were applied in all patients before and after RRT and brain MRI was performed in 7 patients from each group before and after the intervention.

**Results:** Baseline characteristics were similar between groups. Compared to conventional HD, post-dilution HD had longer treatment time and blood volume. There were no significant changes in blood pressure after RRT in both groups. The MMSE test showed no significant differences between groups or within groups. The MOCA test showed an increase in the total score for the post dialution HF group with no significant changes between groups. The magnetic resonance image (MRI) evaluation showed no differences between or within groups.

**Conclusions:** Post-dilution hemofiltration is a safe alternative for the first hemodialysis session in incident RRT; it allows longer treatment time if ultrafiltration is required has a similar neurological risk than conventional HD.

**Hemodialysis and hemodynamic variables.**

Data are shown as mean ± standard deviation, median (percentile 25, percentile 75) or absolute frequency (percentage).

**PO0846**

Intradialytic Yoga-Based Breathing and Relaxation to Improve Anxiety, Depression, and Quality of Life: A Pilot Feasibility Study

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**Background:** In-center hemodialysis patients have high rates of depression and anxiety. Pharmacologic interventions to ameliorate psychological burdens have proven to be limited in efficacy. Alternative therapies are increasingly used for those with chronic disease. A small number of studies have looked at the impact of meditation and yoga to improve symptoms of anxiety and depression and to promote a better quality of life. The aim of this study was to test the feasibility of implementing a chairside intradialytic yoga-based breathing and relaxation technique. A secondary goal was assessing the efficacy of such an intervention.

**Methods:** Eligible subjects were patients with a below average score on the Mental Component Summary (MCS) of a previously completed Kidney Disease Quality of Life (KDQOL™-36) survey both at the start and the end of the study. A Likert scale to measure anxiety was completed at each dialysis treatment both pre- and post-intervention.

**Results:** 11 subjects were enrolled over a 10-month period in 2020; 10 completed the study. As measured by the Likert scale, anxiety was significantly reduced after listening to the recording. Notably, there was a larger reduction in anxiety in patients who started dialysis in the year before the COVID-19 pandemic compared to the pre-pandemic period. Over the study period, there was a significant improvement in the scores of the Effects of Kidney Disease on Quality of Life component of the KDQOL™-36, and a trend toward significant improvement in the Mental Component Summary (MCS).

**Conclusions:** A chairside intradialytic breathing and relaxation program can be integrated into a dialysis treatment session. The study demonstrates an improvement in scores related to anxiety, depression, and measures of quality of life. Larger and randomized trials using this intervention are needed to better understand its benefits and adverse effects, as well as the obstacles to large scale implementation.

**PO0847**

Quality of Life and Symptom Burden Before and After Start of Dialysis in Older Patients

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**Background:** The number of ESKD patients ≥65 starting chronic dialysis increases. Many of these patients have low quality of life (QoL) and high symptom burden. Little is known about the effect of dialysis initiation on QoL and symptoms. Therefore, we studied QoL and symptoms before and after start of dialysis in older patients.

**Methods:** The European Quality (EQUAL) study is an ongoing prospective multicenter cohort study in late stage 4/5 CKD patients ≥65 years. For this analysis, we included all patients who started dialysis. QoL was assessed every 3-6 months using the SF-36, resulting in a physical (PCS) and mental (MCS) component score, with higher scores meaning better QoL. Symptom number and severity were assessed every 3-6 months using the symptom index (DIS), with higher scores meaning higher burden. With linear mixed models we examined the effect of physical QoL, symptom number and severity in the year before and after dialysis start.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: We included 571 older patients at dialysis start. Mean (SD) age was 77 (6) years, 74% were men, 45% had diabetes or cardiovascular disease and mean eGFR was 8.2 (3.7) ml/min/1.73m2. In the year before dialysis MCS decreased by -15.7 (95% CI: -19.5 to -11.8), PCS by -12.0 (-15.7 to -8.2), symptom number increased by +3.5 (±2.5 to +4.0) and severity by +14.8 (+10.9 to +18.8). In the year after, MCS increased by +1.9 (-2.7 to +6.4), PCS decreased by -2.1 (-6.9 to +2.7), symptom number by -0.9 (-2.1 to -0.3) and severity by -6.0 (-10.4 to -1.7).

Conclusions: Mental and physical QoL, symptom number and severity, worsened considerably in the year before dialysis, but stabilized after dialysis initiation. These results could inform older ESKD patients who consider starting dialysis.

PO0849
Fetal and Non-Fetal Gastrointestinal Events with Sodium Polystyrene Sulfonate Use in Hemodialysis: DOPPS
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Background: There are increasing concerns regarding the gastrointestinal (GI) safety of sodium polystyrene sulfonate (SPS), a medication commonly used in the management of hyperkalemia. The objective is to compare the risk for fatal, non-fatal and their composite GI events following initiation of SPS in patients on hemodialysis compared to non-use.

Methods: An international registry of adults (≥18) on chronic intermittent hemodialysis (Dialysis Outcomes and Practice Patterns Study, DOPPS, Phases 2-6 from 2002 to 2018, 17 countries, n=229,295) who were prescribed SPS (n=24,668, 10.76%) were compared with non-users of SPS. Individual patient and facility-level analysis of fatal and non-fatal GI events were examined using weighted models.

Results: Country-level variation in SPS use ranged from 0.74% (UK) to 47.42% (France). 934 fatal, and 837 non-fatal events occurred [3-year cumulative incidence for fatal GI events: SPS 9.0% vs. no SPS 7.6%; non-fatal: SPS 0.4% vs. non-use 0.3%]. The weighted risk of fatal and composite GI events was elevated with SPS use compared to non-use (fatal HR 1.18 95%CI 1.05-1.32, non-fatal HR 0.73 95%CI 0.64-0.84, composite HR 1.02 95%CI 0.82-1.26). Younger age (<65), men, country (France, Belgium, Japan), dialysis vintage (>4 years), shorter HD treatment time (<3.5 hours) and a higher K gradient (serum potassium – dialysate potassium) were associated with a higher risk of a fatal GI event with SPS. The findings were consistent when limited to individuals with known vascular access (n=135, 62% ) and in an analysis examining the fraction of SPS use by facility.

Conclusions: SPS use in patients on hemodialysis is associated with a higher risk of fatal GI events.

Funding: Private Foundation Support

PO0850
Improved One-Year Survival and Decreased Hospitalization Rate in Incident Hemodialysis Patients with Incremental as Compared to Standard Hemodialysis Regimen: A Single-Centre Experience
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Background: Preservation of residual kidney function (RKF) in maintenance hemodialysis (HD) patients is associated with better survival and quality of life. RKF may be better preserved with an incremental HD regimen in patients starting HD. Since 2013, incremental HD (frequency < 3x/week) has been used in our center.

Methods: Incremental HD is implemented in incident HD patients who have a daily residual diuresis > 600 ml, a urea clearance ≥ 2 ml/min and an interdialytic weight gain < 2.5 kg. Patients are clinically assessed every week and a 24 hr-urine sample is collected every other month in order to measure RKF.

Results: From January 2013 to March 2020, 295 patients started chronic dialysis in our center, of whom 221 were on hemodialysis. Among them, 63 patients started maintenance HD with an incremental regimen. These patients did not differ significantly from those with a thrice-weekly HD regimen in terms of age, gender and comorbidity score. Residual diuresis, eGFR and urea clearance at incremental HD initiation were respectively 1842 ± 749 ml/day, 6.7± 3.1 ml/min and 4.0 ± 1.8 ml/mm. Among those 63 patients, four could retrieve a sufficient RKF to become dialysis-independent after a mean 6-month duration of incremental HD and 2 were transplanted while on incremental dialysis. Among the remaining 57 patients, mean duration of incremental HD until transition to a thrice-weekly HD regimen or death was 12 ± 12 months (median, IQR: 10, 6-20). Within the first dialysis year, survival and hospital-free days (median, IQR) were higher in patients starting with incremental HD than in patients with a thrice-weekly HD regimen (91 vs 77%; p=0.02 and 344 (318-360) vs 338 (295-354) days; p=0.03).

Conclusions: These preliminary results show that incremental HD can be implemented in incident HD patients as long as regular clinical and RKF assessments are performed adequately. However, randomised clinical trials assessing long-term survival and quality of life in incremental HD are necessary prior to its large-scale implementation.

PO0851
Association Between Systolic Blood Pressure Changes and Residual Kidney Function Decline Among Hemodialysis Patients After 1 Year
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Background: For patients undergoing hemodialysis, large changes in systolic blood pressure (SBP) from before to after the dialysis has been associated with worse survival. Declines in residual kidney function has also been associated with worse survival. However, the association between SBP changes and residual kidney function decline has not yet been examined.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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293
Methods: We constructed a retrospective cohort of 6659 hemodialysis patients who started dialysis between 2007 and 2011 with baseline changes in SBP and renal urea clearance (KRU) at the 1st and 5th patient quarter (91 day interval from dialysis start). KRU difference was measured as KRU difference between 5th minus 1st patient quarter. The association between baseline average changes in SBP and KRU difference was examined using linear regression analyses. Covariates included age, sex, race, BMI, dialysis modality type, and comorbidities.

Results: Linear regression analysis indicated a linear relationship between change in SBP in KRU and decline even after adjusting for covariates. Trends across all models showed hemodialysis patients with increased systolic blood pressure showed increased residual kidney function compared to the reference (-10 to -0 mmHg). After adjusting for covariates, hemodialysis patients with SBP levels that increased by 10mmHg or more had the greatest increase of KRU (0.12, 95% CI (-0.39, -0.62)), while patients with a decrease of SBP by 10-20mmHg had the greatest decline (-0.31, 95% CI (-0.60, 0.02)). Models adjusting for SBP measures showed similar trends, while the model without low-SBP and post-SBP showed an increased in KRU when SBP decreased by 10-20mmHg (0.23, 95% CI (0.01, 0.05)).

Conclusions: Increase in SBP was associated with a greater KRU decline in hemodialysis patients. Further studies should examine the underlying causes of this association and determine if modifications to dialysis treatments can improve preserving KRU and patient survival.

PO0853
Variability of Plasma Refill Rate and Risk of Intradialytic Hypotension During Maintenance Hemodialysis
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Background: Continuous hemotocrit data can be combined with time-updated ultrafiltration data to non-invasively estimate a semi-instantaneous plasma refill rate (PRR) throughout hemodialysis. The PRR is a dynamic metric that varies throughout hemodialysis, even during periods of constant rates of ultrafiltration, and is influenced by oncotic and hydrostatic forces. We aimed to determine whether variability in PRR is associated with intradialytic hypotension (IDH).

Methods: We used data from continuous hemotocrit monitoring performed at 17 dialysis units from January 2017-October 2019 to calculate intradialytic plasma refill rates standardized to weight and height. PRR variability was defined as the coefficient of variance in PRR (PRRcov) every 15 minutes and categorized into three groups: low (PRRcov < 0.1), moderate (PRRcov 0.1-0.2) and high (PRRcov > 0.2). IDH was defined in three ways: (1) nadir systolic blood pressure (SBP) < 90 mmHg, (2) SBP < 90 mmHg or associated symptoms, and (3) either drop in SBP of 20 mmHg or mean arterial blood pressure of 10 mmHg with associated symptoms. Cox proportional hazard regression was used to assess the impact of starting PRR variability on time to first IDH. Marginal structural modeling was used to assess the impact of time-updated plasma refill rate variability on the risk of IDH.

Results: Among 2350 patients and 184,453 hemodialysis sessions, mean session time was 220 ± 26 min and ultrafiltration rate was 9.0 ± 3.3 ml/kg/min. Median PRRcov was 1.20 (IQR 0.68, 2.18) across all sessions. Compared to hemodialysis sessions with low PRRcov sessions with high PRRcov in the first 15 minutes of treatment were associated with a 1.14 hazard of intradialytic hypotension (95% CI 1.05, 1.24). Accounting for repeated measures and changes in systolic blood pressure and ultrafiltration, sessions with high PRRcov throughout the duration of hemodialysis were associated with an increased risk of IDH based on a definition 1 OR 1.29, 95% CI 1.16, 1.43). For definition 2 (OR 1.85, 95% CI 1.77, 1.94) and definition 3 (OR 1.87, 95% CI 1.78, 1.98).

Conclusions: PRR variability was associated with higher risk of IDH, independent of time-varying confounding from SBP and UFR. PRR variability could be a promising bedside metric for hemodynamic instability during hemodialysis.

Funding: NIDDK Support.

PO0854
Systemic Parameters of the Renin-Angiotensin-Aldosterone System Remain Unaffected by Changes in Fibroblast Growth Factor 23 Levels Across Hemodialysis Patients
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Background: Fibroblast growth factor 23 (FGF23) is elevated in patients with chronic kidney disease and promotes the development of left ventricular hypertrophy (LVH). Decreasing the levels of FGF23 with the calcimimetic drug etelcalcetide can abate these changes in hemodialysis patients. Whether the antihypertrophic effect of FGF23 is modified by the renin-angiotensin-aldosterone system (RAAS) is unknown. The aim of the analysis was to determine whether changes in FGF23 levels are associated with differences in RAAS-parameters in hemodialysis patients, possibly explaining its influence on LVH.

Methods: Serum samples were obtained at baseline and one year from participants in the randomized EtECAR-HD trial. In this study 62 hemodialysis patients were treated with either calcimimetic or vitamin D treatment, which have opposite effects on FGF23. We analyzed PRA-S as the angiotensin-based marker for renin activity, angiotensin II (AngII), angiotensin-converting enzyme-2 (ACE2) and aldosterone using a high throughput mass spectrometry assay.

Results: The median levels of FGF23 were 2386 pg/ml (1st to 3rd quartile 819–1566) and 1386 pg/ml (288–4068) at baseline and end of study, respectively. The association of changes between baseline and end of study in FGF23 with the levels of the RAAS-components (i.e. PRA-S, AngII, ACE2, aldosterone) estimated by linear regression models was weak, with effect sizes for log2-fold-change in FGF23 close to zero. The median overall levels of PRA-S were 130 pg/ml (1st to 3rd quartile 76-269), of AngII 137 pg/ml [76-201], of aldosterone 335 pg/ml [139-454], of ACE2 1.38 ng/ml (1.1-1.8), as compared with healthy controls (PRA-S 196 pg/ml [98-238], AngII 137 pg/ml [76-201], aldosterone 335 pg/ml [139-454], ACE2 1.17 ng/ml [1.1-1.65]).

Conclusions: In the present study we were able to show that systemic RAAS activity was grossly unaffected by the treatment induced changes in FGF23 levels in this cohort. Overall, the levels of PRA-S, AngII and aldosterone were well below the ranges measured in healthy controls suggesting that the RAAS is not systemically activated in hemodialysis patients.

Funding: Commercial Support - Investigator-initiated research grant from Amgen.
**Prediction of Left Ventricular Function Using Electrocardiogram Data in Patients on Hemodialysis**

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**Background:** Left ventricular (LV) systolic dysfunction is common in patients on maintenance hemodialysis (HD). Early identification of patients with depressed left ventricular ejection fraction (LVEF) can facilitate disease modifying treatment. Electrocardiograms (ECGs) are routinely performed in patients on HD, however they have not been used for estimating LVEF in this population.

**Methods:** We analyzed data from five Mount Sinai facilities. Patients on HD with a transthoracic echocardiogram within 7 days of an ECG were identified using diagnostic and procedure codes. ECG data were preprocessed to remove recording artifacts, plotted to an image, and along with patient demographics were analyzed using a model comprised of a Multi-Layer Perceptron and a Convolutional Neural Network. We developed three models: 1) trained from scratch in only HD patients, 2) pre-trained on natural images (Imaginet), and 3) pre-trained on all LVEF-ECG pairs (n=698,890) excluding those for ESRD patients. Models 2 and 3 leverage transfer learning, which reuses knowledge gained from a task to perform a similar task. All models were trained/tested on LVEF-ECG pairs for ESRD patients within a Group Stratified K Fold (K=5) Cross Validation design, and performance was compared per Area Under Receiver Operating Characteristic curve (AUROC) for each category of LVEF ≥40%, 41 to ≤50%, and >50%.

**Results:** We extracted 18,626 LVEF-ECG pairs for 2,168 ESRD patients. For detection of LVEF ≤40%, models trained from scratch and pre-trained on Imaginet had AUROCs of 0.74 (95% CI: 0.67-0.80) and 0.71 (95% CI: 0.65-0.77) respectively. These were outperformed by the model pre-trained on ECG data [AUROC of 0.91 (95% CI: 0.88-0.93)]. Similar results were seen at detection of LVEF ≥40% with the AUROC being 0.85 (95% CI: 0.89-0.96) for both the model trained from scratch and the Imaginet model, while the model pre-trained on ECG data achieved an AUROC of 0.82 (95% CI: 0.78-0.87).

**Conclusions:** A model pre-trained on non-HD LVEF-ECG pairs using transfer learning performed better than output models trained from scratch or pre-trained on Imaginet. This model facilitates identification of LV systolic dysfunction in patients on HD.

PO0858

**Clinical Outcomes of Bioimpedance Analysis-Guided Hemodialysis: A Meta-Analysis of Randomized Controlled Trials**

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**Background:** Determination of fluid status in hemodialysis patients could be a great challenge for providers. Body composition monitoring using bioimpedance analysis (BIA) is an emerging tool in guiding fluid removal in hemodialysis population. However, although there are some randomized controlled trials (RCT), the reported outcomes remain heterogeneous and inconclusive across studies.

**Methods:** Ovid MEDLINE, EMBASE, and the Cochran Library were searched for eligible articles through May 2021. Inclusion criteria were: 1) RCT comparing BIA against clinical assessment, 2) sample size ≥ 50, 3) adults ≥ 18 years on hemodialysis (HD), 4) clinical outcomes were reported. No publication bias detected by Egger's regression intercept analysis.

**Results:** A total of seven RCTs (n = 1029 total; 519 BIA, 510 control), dated from 2010 to 2019, with a mean follow-up duration of 15.0±6.10 months were identified. There was no difference in mortality between BIA and clinical group (odds ratio [OR] 0.79; 95% CI 0.431, 1.472; I2 12.5%). BIA group had significantly lower weight change during follow-up duration compared to clinical group (standard means difference [SMD] -0.270; 95% CI -0.532, -0.018; I2 9.6%). Clinical group had significantly higher systolic blood pressure compared to BIA group (SMD 0.157; 95%CI 0.034, 0.280; I2 12.3%) with a mean difference of 0.052 mmHg (95% CI 0.513, 0.532; I2 0%). Clinical group had significantly higher diastolic blood pressure compared to BIA group (SMD 0.217; 95%CI 0.105, 0.326; I2 52.8%). Clinical group had significantly higher pre-HD body weight (SMD 0.280; 95% CI 0.130, 0.430; I2 48.1%) with a mean difference of 0.370 kg (95% CI 0.178, 0.563; I2 47.8%) compared to BIA group. There was no difference in post-HD body weight between the two groups (SMD 0.156; 95% CI 0.005, 0.306; I2 0%).

**Conclusions:** There was no mortality benefit to BIA-guided HD compared with clinical-guided HD. However, BIA-guided HD improved systolic blood pressure and weight gain compared to clinical-guided HD. Pulse wave velocity, which represents arterial stiffness, was also lower in BIA group. Although our findings suggest some non-mortality benefits to BIA-guided HD, however, the clinical impact of BIA-guided HD on cardiovascular events, intradialytic complications, and patients' quality of life remain to be elucidated in future RCTs.

**Point-of-Care Ultrasound Measurements to Predict Intradialytic Hypotension: A Cross-Sectional Pilot Study**

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**Background:** Intradialytic hypotension (IDH) results from excessive ultrafiltration in patients on chronic hemodialysis (HD) and has been linked to increased mortality. Prescribing the right amount of ultrafiltration can be challenging, partly due to the poor sensitivity of physical examination for detection of volume overload in HD patients. POCUS is emerging as a valuable tool in the assessment of volume status. The goal of this study is to determine whether pre-dialysis POCUS measurements are associated with development of IDH.

**Methods:** Patients >18 years old on HD for at least 6 months and ordered for 2 or more liters of ultrafiltration were included. Two blinded POCUS-trained physicians obtained the following measurements within the first 30 minutes of HD: left ventricular septal and lateral E/e’, portal vein (PV) pulsatility and IVC size. The primary outcome was development of IDH events or post HD orthostasis. IDH was defined as a decrease in systolic blood pressure by ≥ 20 mmHg plus symptoms of IDH. Fischer’s and Mann Whitney tests were used to examine the association between IDH events and various demographic, clinical, and POCUS related parameters.

**Results:** There was no association between age, sex, ethnicity, BMI, dialysis vintage, Charlson comorbidity index, interdialytic weight gain, IVC size, PV pulsatility, septal E/e’ and the primary outcome. There was a significant association between lateral E/e’ and IDH events or post HD orthostasis (p=0.05).

**Conclusions:** In this pilot study, an elevated lateral E/e’ was associated with lower rates of HD events or post HD orthostasis. The role of POCUS in guiding fluid removal during HD warrants further exploration.
PO0859
Relationship Between Fluid Overload and Hemoglobin Concentration in Hemodialysis Patients: A Longitudinal Analysis
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Background: Quantification of fluid status by bioimpedance spectroscopy (BIS) has become routine outside United States (US). We performed the first assessment of fluid status in US hemodialysis (HD) clinics using a BIS device. We studied the longitudinal association between fluid overload (FO) and hemoglobin (Hgb) concentration adjusting for inflammation and erythropoiesis-stimulating agents (ESA).

Methods: Measurement of FO [Body Composition Monitor (BCM); Fresenius Medical Care] was conducted cross-sectionally in chronic HD patients in 4 HD clinics in New York. We built linear mixed effects models with Hgb as the dependent variable and calculated FO longitudinally to include as a fixed effect. We tested the robustness of the association to account for the influence of inflammation by including the neutrophil-lymphocyte ratio (NLR) as an additional fixed effect. As a subset analysis 2 separate models were built in subjects with or without ESAs. To corroborate the dilutional effect of FO we exchanged Hgb for albumin as a fixed effect.

Results: We studied 169 patients (Figure 1). FO was inversely associated with Hgb [Estimate -0.16 (-0.20 to -0.12) g/dl per 1L of FO], a significant fixed effect that remained unchanged in magnitude even after inclusion of NLR [Estimate 0.04 (-0.05 to 0.06) g/dl per 1 unit of NLR]. The effect was larger in patients without ESA prescription [Estimate -0.22 (-0.32 to -0.12) g/dl per 1L of FO]. FO was a significant determinant of albumin [Estimate -0.02 (-0.03 to -0.01) g/dl per 1L of FO] with NLR being a significant fixed effect [Estimate -0.03 (-0.04 to -0.01) g/dl per 1 unit of NLR].

Conclusions: Hgb is inversely affected by FO, a significant effect independent of inflammation (NLR). The impact of FO on Hgb concentration is larger in those with no ESA treatment emphasizing that fluid status has to be considered in anemia management. The effect of FO on albumin supports hemodilution as the principal cause for the changes seen on Hgb.

Funding: Commercial Support - Fresenius Medical Care

PO0860
Interpreting Home Blood Pressure Measurements in Haemodialysis: A Post Hoc Analysis of a Randomized Cross-Over Study
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Background: Home BP correlates better with ambulatory BP, target organ damage and mortality in dialysis patients. We aimed to determine the agreement of in-centre BP with home BP.

Methods: A post-hoc analysis of a pilot-scale, randomised two-period cross over study comparing self-monitoring of BP over 4 weeks with usual care in 41 haemodialysis patients. www.clinicaltrials.gov. NCT0340349. Dialysis clinic BP and home BP (using average real variability (ARV). Mixed effects models for repeated measures with a moving average window of 2 weeks were used to examine associations with BP and ARV.

Results: 33 out of 41 participants had sufficient home BP measurements for inclusion (mean age 63.7 years, 52.1% male). Post-dialysis SBP had moderate agreement with in-home SBP measurements (K = 0.6) compared with pre-dialysis SBP measurements (K = 0.4). The mean bias between home SBP and post SBP measurements was -4.15 mmHg (95% CI 23.5 to -31.8 mmHg) (Figure 1). Home SBP ARV (16 +/- 5) was as high as pre SBP ARV (14 +/- 5) and post SBP ARV (13 +/- 5). In univariate analysis only calcium channel blockers were consistently associated with pre-dialysis (P = 0.02), post-dialysis and home SBP (both P<0.001).

Conclusions: Post-dialysis SBP demonstrates moderate agreement with home BP when two week BP averages are used. Home BP measurements are as variable as clinic BP measurements and isolated measurements may lack interpretability. Averaging the home BP over two weeks may improve the utility of home BP monitoring.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

PO0861
Increased Tricuspid Regurgitation Jet Velocity as a Predictor of Acute Decompensated Heart Failure in ESRD Patients on Maintenance Hemodialysis
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Background: Many patients with end-stage renal disease (ESRD) on hemodialysis (HD) experience left ventricular hypertrophy and reduced vascular compliance and are likely to develop heart failure (HF). We aimed to determine the hemodynamic factors associated with acute decompensated events among ESRD patients undergoing HD.

Methods: We retrospectively investigated ESRD patients on HD through a medical record review. We excluded patients with significant ischemic heart disease (IHD), percutaneous coronary intervention or coronary artery bypass graft, significant valvular heart disease (VHD), or malignancy. We divided patients into those experience who experienced any admission due to acute decompensated HF (ADHF) and those who did not.

Results: Of the 188 ESRD patients on HD, 87 were excluded, and 101 were enrolled (mean age: 63.7 years, 52.1% male). The ADHF group demonstrated significantly higher tricuspid regurgitation (TR) jet velocity (2.9 ± 0.6 vs. 2.5 ± 0.4 m/s, respectively; p=0.004) than the non-ADHF group. Multivariate logistic regression analysis demonstrated that TR jet velocity (odds ratio: 8.356, 95% confidence interval: 1.806-38.658; p=0.007) was an independent predictor of ADHF after adjusting for age and sex, while LVEF and E/E’ were not. Per receiver operating characteristic curve analysis, TR jet velocity > 2.8 m/s was associated with ADHF with 47.7% sensitivity and 76.4% specificity (area under the curve: 0.656).

Conclusions: Our data showed that increased TR jet velocity was an independent predictor of ADHF events in ESRD patients on HD, but LVEF and E/E’ were not.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>25%</th>
<th>75%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (13.7)</td>
<td>62</td>
<td>50</td>
<td>78</td>
<td>0.029</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57 (52.1)</td>
<td>55</td>
<td>41</td>
<td>71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>48 (43.5)</td>
<td>45</td>
<td>32</td>
<td>60</td>
<td>0.367</td>
</tr>
<tr>
<td>DM (%)</td>
<td>35 (40.5)</td>
<td>30</td>
<td>20</td>
<td>45</td>
<td>0.831</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>8 (8.9)</td>
<td>7</td>
<td>4.5</td>
<td>13</td>
<td>0.790</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49 (17.6)</td>
<td>45</td>
<td>30</td>
<td>55</td>
<td>0.129</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>174 (22)</td>
<td>160</td>
<td>140</td>
<td>190</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>92 (18)</td>
<td>85</td>
<td>70</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, pred. HD (kg)</td>
<td>75 (18.2)</td>
<td>70</td>
<td>60</td>
<td>85</td>
<td>0.139</td>
</tr>
<tr>
<td>Body weight, post. HD (kg)</td>
<td>75 (18.2)</td>
<td>70</td>
<td>60</td>
<td>85</td>
<td>0.139</td>
</tr>
<tr>
<td>Diuretics use (%)</td>
<td>54 (51.7)</td>
<td>50</td>
<td>40</td>
<td>60</td>
<td>0.178</td>
</tr>
<tr>
<td>HDWG, kg</td>
<td>-2.3 (1.6)</td>
<td>-5</td>
<td>-10</td>
<td>0</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Baseline characteristics
PO0862
Benefit of More Frequent Dialysis on Dialysis Recovery Time in Nursing Home Patients with ESRD
Alice Hellebrand,1 Eran Y. Bellin,1,2 Steven M. Kaplan,1 Jordan Ledvina,1 William Markis,2 Nathan W. Levin,2 Allen Kaufman,1 Dialyze Direct Brooklyn, Brooklyn, NY; 2Albert Einstein College of Medicine, Bronx, NY.

Background: Dialysis patients admitted to a skilled nursing facility (SNF) are characterized by advanced age, frailty, and multiple comorbidities. Based on prior studies, which demonstrated shortened dialysis recovery time (DRT) with more frequent dialysis (MFD) in populations aged ~50s living at home (FREEDOM Study 2010, FHN trial 2006), it was postulated that dialysis patients in a SNF would benefit from MFD.

Methods: Patients studied were admitted to SNFs in OH, TX, FL, NY, and PA from November-December 2019 (pre-COVID) and could reliably answer questions about DRT. 80% were undergoing subacute rehabilitation and 20% were permanent residents of the SNF. Patients received NxStage on-site staff assisted MFD 5x (80%) or 4x (20%) per week. MFDV (V/>2.1. At every dialysis, patients were asked by their RN caregiver “How long did it take you to recover from your last HD session?” Responses were deemed unreliable if a patient had cognitive impairment. Reliable responses were used for outcome analysis. In the present study, DRT data was collected by a caregiver nurse, differing from the methodology of the FREEDOM/FHN studies which collected DRT data via KDQOL form or phone interview. The implications of these differences in data collection methods are currently unknown.

Results: 485 unique patients were included in the study. Demographics included 53% males, mean age 67.5 +/- 13 years, African American 19%, Caucasian 25%, Hispanic 5%, Asian 0.4%, unknown or other 51%. Mean DRT was 1.5 +/- 2.6 hours. Mean DRT was calculated using the midpoint recovery time for intervals, or 18 hours when DRT was the next morning or beyond. In 69%, DRT was < 2 hours.

Conclusions: In the FREEDOM and FHN conventional HD 3x per week study arms, DRT averaged 6-8 hours. MFD reduced DRT to ~1.0 hour in those relatively young patients living at home. In our study, HD patients residing in a SNF and receiving MFD experienced DRT of 1.5 hours. Age, frailty and comorbid conditions therefore do not prevent DRT benefits of MFD. DRT benefits could stem from more effective, gentler fluid management by MFD. Further studies are needed to fully explore the impact of shortened DRT on rehabilitation scores, hospitalizations and deaths in elderly patients residing in SNFs.

Funding: Commercial Support - Dialyze Direct

PO0863
The Combination of Arterial Stiffness and Peripheral Vascular Disease Aggravates Survival Among Hemodialysis Patient Using Competing Risk Analysis
Adisorn Pathumrak,1 Kanin Thammavarunucut, Chaggiya Kitayakara, Arkorn Nongmuang, Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.

Background: The survival in end stage renal disease (ESRD) patient is unacceptable high. The Skin autofluorescence (SAF) for advance glycation end products (AGEs), peripheral vascular disease (PVD) (ankle-brachial index, ABI ≤0.9) and arterial stiffness (cardio ankle vascular index, CAVI>9) were reports as predictors of mortality. However, kidney transplantation (KT) competes the mortality outcome. We aim to explore these markers for precisely prediction of mortality using competing risk method.

Methods: Retrospective chart review in chronic hemodialysis patients was done in 3 hemodialysis centers in North Bangkok during November 2015 and March 2016. Arterial stiffness, SAF, IMAR and PVD were collected as a clinical predictor. Cumulative incidence of mortality was used as was a primary outcome. Logistic regression with competing risk model was used to analyze the factor affecting mortality.

Results: A Total of 176 patients were eligible and classified into 4 groups according to PVD and stiffness status. During follow up 44.5±14.8 months, the overall mortality rate was 27% which is 13.2, 28.6, 31.5 and 61.9% in no PVD and stiffness, exclusively PVD, exclusively stiffness, and combine group respectively. The PVD (HR 2.93, CI 1.2 to 7.14, P=0.018) and stiffness (HR 2.57, CI 1.1 to 5.73, P=0.021) were independent predictors of mortality. In competing risk method, the combination of PVD and stiffness associate with highest mortality (P=0.0002139), while the patients who no PVD and stiffness had the highest rate for KT (P=0.0050275).

Conclusions: The PVD and stiffness were an independent risk of mortality among hemodialysis patients. The combination of PVD and stiffness may stratify risk of mortality in hemodialysis patient using competing risk method.

PO0865
Consistency of the Dry Weight of Hemodialysis Patients Predicted Using Bioelectrical Impedance Analysis Between Standing and Lying-Down Positions
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Background: Accurate dry weight (Dw) estimation is important for hemodialysis patients. Although bioimpedance spectroscopy (BIS) is commonly used to measure Dw, the BIS-based Dw frequently differs from the clinical Dw.

Methods: We analyzed the characteristics of patients whose BIS-based Dw were over- and underestimated. In this retrospective cohort study, we evaluated 1,555 patients undergoing maintenance hemodialysis in Chungham National University Hospital. The gap (Dwclinical-DwBIS) was calculated by comparing the BIS and clinical Dws.

Results: We analyzed the clinical characteristics of patients with positive (n = 835) and negative (n = 720) gaps. Compared with other patients, the Dwclinical-positive group was taller, had higher extracellular water (ECW) level and extracellular/intracellular water index (ECI); and had lower weight, body mass index (BMI), lean tissue index (LTI), fat tissue index (FTI), fat mass (FAT), and adipose tissue mass (ATM), as well as lower levels of hemoglobin, total protein, albumin, and phosphorous. The Dwclinical-negative group exhibited higher levels of hemoglobin, total protein, albumin, and phosphorous, as well as elevated BMI, FTI, FAT, and ATM, however, it had lower height, ECW, and ECI. Linear regression analysis revealed that FAT significantly predicted Dwclinical accuracy.

Conclusions: The clinical Dw of patients with malnutrition and a low fat mass tended to be underestimated, while the clinical Dw of patients with comparatively large fat reserves tended to be overestimated. These characteristics of dialysis patients will aid in the correction of BIS-associated Dw errors.
PO0866

Use of Crit-Line to Reduce Intradialytic Hypotension in Hospitalized Patients Receiving Dialysis

Background: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis in hospitalized patients with acute kidney injury (AKI) and end stage kidney disease (ESKD). Crit-Line is a device that monitors absolute hematocrit and oxygen saturation during dialysis and reads out the percent blood volume change. Whether the use of Crit-Line during HD in hospitalized patients results in less IDH is unknown.

Methods: We performed a time series study in all hospitalized adult AKI/ESKD patients undergoing acute HD at the University of Colorado. During the control period baseline data was collected. During the intervention period, Crit-Line was used on all hospitalized patients undergoing HD including those receiving portable HD treatments in the ICU. During both time periods, nurses recorded number of hypotensive events, patient symptoms and modifications that were made to the dialysis prescription. The primary outcome was number of IDH events defined by the NKF KDOQI Guidelines.

Results: 328 patients were included, 161 from the control period and 167 from the intervention period. Patient characteristics were similar in both time periods and are shown in Table 1. IDH occurred in 23.5% of treatments during the control period and 18.7% during the intervention period, but the difference was not significant, p=0.22 (Figure 1). When examining portable dialysis treatments in the ICU, there was a significant reduction in IDH with Crit-Line compared to control (Odds Ratio 0.71 95% CI 0.51-0.99, p=0.04).

Conclusions: Use of Crit-Line in hospitalized patients undergoing dialysis in the ICU resulted in less IDH.

Funding: Commercial Support - Fresenius Renal Therapies

Table 1. Characteristics of Patients in Control vs. Intervention Periods

<table>
<thead>
<tr>
<th></th>
<th>Control Period (n=161)</th>
<th>Crit-Line Period (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>68 (47.7)</td>
<td>68 (46.7)</td>
</tr>
<tr>
<td>Black (N,N/N)</td>
<td>82 (50.9)</td>
<td>79 (48.1)</td>
</tr>
<tr>
<td>ESKD (%)</td>
<td>14 (17.0)</td>
<td>12 (7.4)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>44 (29.2)</td>
<td>46 (27.4)</td>
</tr>
<tr>
<td>IFE (%)</td>
<td>54 (35)</td>
<td>51 (30)</td>
</tr>
<tr>
<td>Number of dialysations (N/N)</td>
<td>357 (227-431)</td>
<td>321 (245-413)</td>
</tr>
</tbody>
</table>

PO0867

Dry Weight Adjustments for Hemodialysis Patients Using Machine Learning
Hae Ri Kim,1 Jae wan Jeon,1 Youngrok Ham,1 Kiryang Na,2 Kang Wook Lee,2 Yoon-Kyung Chang,2 Dae Eun Choi.1 Chungnam National University Sejong Hospital, Sejong, Republic of Korea; 2Chungnam National University, Daejeon, Daejeon, Republic of Korea; 1Daejeon Saint Mary's Hospital, Daejeon, Daejeon, Republic of Korea.

Background: Knowledge of the proper dry weight plays a critical role in the efficiency of dialysis and the survival of hemodialysis patients. Recently, bioimpedance spectroscopy (BIS) has been widely used for set dry weight in hemodialysis patients. However, BIS is often misrepresented in clinical healthy weight. In this study, we tried to predict the clinically proper dry weight (DW_py) using machine learning for patient’s clinical information including BIS. We then analyze the factors that influence the prediction of the clinical dry weight.

Methods: As a retrospective, single center study, data of 1672 hemodialysis patients were reviewed. DW_py data were collected when the dry weight was measured using the BIS (DW_BIS). The gap between the two (Gap_DW) was calculated and then grouped and analyzed based on gaps of 1 kg and 2 kg.

Results: Based on the gap between DW_BIS and DW_py, 972, 303, and 384 patients were placed in groups with gaps of <1 kg, ≥1kg and <2 kg, and ≥2 kg, respectively. For less than 1 kg and 2 kg of Gap_DW, it can be seen that the average accuracies for the two groups are 83% and 72%, respectively, in using XGBoost machine learning. As Gap_DW increases, it is more difficult to predict the target property. As Gap_DW increases, the mean values of hemoglobin, total protein, serum albumin, creatinine, phosphorus, potassium, and the fat tissue index tended to decrease. However, the height, total body water, extracellular water (ECW), and ECW to intracellular water ratio tended to increase.

Conclusions: Machine learning made it slightly easier to predict DW_py based on DW_BIS under limited conditions and gave better insights into predicting DW_CFR Malnutrition-related factors and ECW were important in reflecting the differences between DW_BIS and DW_CFR.

PO0868

Interdialytic Weight Gain in Long Intervals and Mortality Among Maintenance Hemodialysis Patients
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Background: Interdialytic weight gain (IDWG) is an important factor for sudden death on the first dialysis day right after long interdialytic intervals (i.e. 2-day breaks between dialysis treatments) in hemodialysis patients. We defined IDWG in long intervals (IDWGL) as the IDWG during 2-day breaks. In this study we examined the association between IDWGL and medium-term mortality.

Methods: This retrospective cohort study included patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between seven categories of IDWGL and all-cause mortality using Cox regression model. Seven categories of IDWGL were as follows: 0<−1%, 1−<2%, 2−<3%, 3−<4%, 4−<5%, 5−<6%, and ≥6%. We also examined continuous associations between IDWGL and mortality using restricted cubic spline analysis.

Results: We examined mortality in 35225 patients. The mean age (and standard deviation) was 62±15 years, and 8112 died during the median follow-up period of 1.4 years. Higher categories of IDWGL were associated with increased risk of mortality. The hazard ratios (95% confidence intervals) of all-cause mortality for 3−<4%, 4−<5%, 5−<6%, and ≥6% were 1.09 (1.03-1.16), 1.14 (1.06-1.23), 1.17 (1.06-1.29), and 1.25 (1.14-1.38) (Reference: 2−<3%) (Figure a). The restricted cubic spline analysis showed that risk of mortality increased when IDWGL exceeded 2% (Figure b).

Conclusions: IDWGL exceeded 2% was associated with higher risk of mortality. Our results suggest IDWGL can be a risk parameter for medium-term mortality.

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Underline represents presenting author.
PO0869
Coronary Artery Calcification Is a Risk Factor for Intradialytic Hypotension in Hemodialysis Patients
Sonoo Mizui,1 Yoshiko Nishizawa,1 Toshiki Doi,1 Kazuomi Yamashita,1 Kenichiro Shigemoto,1 Koji Usui,2 Michiko Arita,3 Takayuki Naito,4 Shigehiro Doi,5 Takao Masaki5 1Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; 2Hiroshima Daigaku Byoin, Hiroshima, Japan; 3Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; 4Ichiyokai East Clinic, Hiroshima, Japan; 5Ichiyokai Yokogawa Clinic, Hiroshima, Japan.

Background: Vascular calcification and intradialytic hypotension (IDH) share common risk factors in hemodialysis (HD) patients, but there are few reports about the association. We investigated the association between IDH and coronary artery calcification (CAC) and their effects on mortality in HD patients.

Methods: Subjects were consecutive maintenance HD patients. IDH was defined as nadir systolic blood pressure <100 mmHg, or the requirement for bolus infusion of saline and vasopressor (ethylene glycol solution) during at least two of 10 HD sessions. Laboratory data and Agatston coronary artery calcium score (CAC) were obtained at baseline. Logistic regression analyses for CACs and Cox analyses for mortality were conducted.

Results: In all subjects (n=173), age and dialysis vintage were 66±12 years and 102±9 months, respectively. IDH occurred in 37 patients (21.4%), and CACs was higher in the IDH group than in the non-IDH group [1,845 (243–3,774) vs. 884 (161–2,465)]. IDH was significantly (P<0.05) associated with CACS [odds ratio (OR): 1.01], diabetes (OR: 2.98), mean predialysis systolic blood pressure (OR: 0.93), mean ultrafiltration (P<1.92), K/Vurea (OR: 11.27) and erythropoietin responsive index (ERI) (OR: 0.91), but not with serum albumin or use of calcium channel blockers. For 3-year all-cause mortality, the cut-off value of CACs, determined by receiver operating characteristics curve analysis, was 1,829 with sensitivity of 69% and specificity of 77%. Of the 173 subjects, 45 all-cause mortality and 19 cardiovascular events occurred for 3 years. Patients with both IDH and CACs ≥1,829 had the highest 3-year cumulative CV death rate (33.3%, P<0.01) compared with 19.7%, 11.5%, and 4.5% in those with CACs ≥1,829 only, IDH only, and neither, respectively. In Cox models including age, sex, diabetes, albumin, phosphate, CRP, ERI and FGF23, hazard ratios (HRs) for 3-year all-cause mortality of IDH, CACs ≥1,829, or IDH or CACs ≥1,829 were similar, but HR for 3-year CV mortality was the highest in CACs with ≥1,829 (OR: 0.01) compared with 7.29 (P<0.01) and 6.77 (P<0.01), in those with CACs ≥1,829 only, and IDH only. CACs ≥1,829 independently predict CAC risk for HD patients, and CACs provide additional risk discrimination over IDH for CV mortality in HD patients.

Funding: Private Foundation Support

PO0870
Cardiac Arrests During Hemodialysis Among Maintenance Hemodialysis Patients in a Large Dialysis Network in India

Background: Cardiac arrest (CA) during a HD session carries a high mortality and is reported associations include age, comorbidity, dialysis characteristics. Since much is unknown in India, we aimed to study Incidence of CA, prediposing factors and outcome of CPCR following intra HD cardiac arrests.

Methods: Consecutive CA in a large dialysis network from July 2019 to March 2020 were reviewed for age, gender, HD frequency, adequacy, vascular access, HD facility location, size, nephrologist coverage, b/o DM and IHD, HD session timing, duration of HD session & hospitalization in recent past & ultrafiltration rate. Survivors vs non-survivors of CPR were compared with t-test, Chi-square test or Fisher’s exact statistic and risk ratio (RR) for significance of associated factors were analyzed using STATA, v 14.2.

Results: 122 CA occurred among 2,981,759 sessions; rate of 1/24441. 71 survived CA were reviewed for age, gender, HD frequency, adequacy, vascular access, HD facility location, size, nephrologist coverage, b/o DM and IHD, HD session timing, duration of HD session & hospitalization in recent past & ultrafiltration rate. Survivors vs non-survivors of CPR were compared with t-test, Chi-square test or Fisher’s exact statistic and risk ratio (RR) for significance of associated factors were analyzed using STATA, v 14.2.

Conclusions: Incidence of CA in India is developed countries experience; larger facilities & smaller cities form a high proportion of events. Age > 80 risk of death. Female, ↓ Hb or adequacy, UFR >10ml/kg/hour, low HD freq in 2 months prior to CA show tendency to higher risk for non survival. Limitation includes lack of analysis of CPR and post CPR hospitalization course

PO0871
Clinical Significance of Plasma Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 Levels to Assess the Cardiovascular Risk in Hemodialysis Patients
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Background: Matrix metalloproteinases (MMPs) are endopeptidases that control extracellular matrix synthesis and degradation. Two MMP subtypes, MMP-2 and MMP-9, are known to play important roles in the development and progression of cardiovascular (CV) disease, but its clinical relevance as predictors of cardiovascular events is unclear in hemodialysis patients.

Methods: We prospectively enrolled 435 patients undergoing maintenance hemodialysis from K-cohort between June 2016 and April 2019. Plasma MMP-2, MMP-9 levels, and several biomarkers were measured at the time of study data entry. Primary endpoint was defined as a composite of cardiovascular events.

Results: Plasma MMP-2 level were increased in patients with incident CV events than those without CV events, whereas plasma MMP-9 levels were not different between groups. MMP-2 levels were positively correlated with circulating cardiac markers including brain natriuretic peptides (BNP), N-terminal proBNP, and heart-type fatty acid binding protein. The cumulative event rate of the composite of CV events was significantly greater in patients with higher MMP-2 tertile 3 than in those with other MMP-2 tertile 1 (p = 0.015). MMP-2 tertile 3 was associated with a 2.77-fold higher risk of the composite of CV events (95% CI, 1.40–5.45) and 4.67-fold higher risk of cardiac events (95% CI, 2.06–10.56) after multivariable adjustments. However, plasma MMP-9 levels were not positively correlated with circulating cardiac markers, and not associated with risk of incident CV events.

Conclusions: Higher plasma MMP-2 levels, but not MMP-9 levels, had the positive relationship with circulating levels of cardiac pathology markers, and were associated with increased risks of incident CV events and cardiac events among hemodialysis patients.

PO0872
Utility of CHA2DS2-V ASc score to Predict Mid-Term Clinical Outcomes in Hemodialysis Patients
Aiko Okubo,1 Toshiki Doi,1,2 Yoshiko Nishizawa,1 Kenichiro Shigemoto,1 Sonoo Mizui,1 Takao Masaki,1 Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; 2Ichiyokai Yokogawa Clinic, Hiroshima, Japan.

Background: The CHA2DS2-V ASc score has been widely used as a predictive score for stroke in patients with atrial fibrillation (AF). Recently, it was reported that the CHA2DS2-V ASc score is useful for predicting cardiovascular disease (CVD) or all-cause mortality in patients with or without AF. However, few reports have examined the association between this score and mortality in hemodialysis patients.

Methods: We analyzed 525 consecutive patients who started hemodialysis at our facilities from March 2006 to October 2017. CHA2DS2-V ASc score was calculated at time of initiation of hemodialysis. Multivariate Cox proportional hazards analysis was used to assess independent risk factors for 3-year all-cause mortality.

Results: During the 3-year follow-up period, 153 (29.1%) patients died (cardiovascular death, n=88). According to multivariate analysis, serum albumin [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.43–0.89, P=0.01], creatinine (HR 0.81, 95% CI 0.71–0.99, P=0.04), and CHA2DS2-V ASc score (HR 1.31, 95% CI 1.21–1.46, P<0.001) were associated with 3-year all-cause mortality. Patients with CHA2DS2-V ASc score ≥4 had higher risk of all-cause and CVD mortality than those with CHA2DS2-V ASc score <4 (all-cause mortality: HR 2.20, 95% CI 1.42–3.71, P=0.015; CVD mortality: HR 2.83, 95% CI 1.37–5.44, P<0.001).

Conclusions: The CHA2DS2-V ASc score is a useful predictor of 3-year all-cause and CVD mortality in incident hemodialysis patients.
NT-ProBNP for Heart Function and Volume Status in Hemodialysis Patients
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Background: N-terminal pro brain natriuretic peptide (NT-proBNP) is a biomarker that predicts heart failure and evaluates volume status in Hemodialysis (HD) patients. However, it is difficult to determine the cutoff value of NT-proBNP in HD patients. In this study, we analyzed whether NT-proBNP helps with predicting heart function and volume status in HD patients.

Methods: Retrospective study was conducted on 96 end-stage renal disease patients with HD. All patients underwent echocardiography and Bioelectrical Impedance Analysis (BIA) after a post HD session. Overhydration (OH) was measured by BIA. Laboratory data were obtained on preHD during the mid-week HD sessions. Serum NT-proBNP was measured after HD.

Results: There was an inverse correlation between NT-proBNP and ejection fraction (EF) (β = -0.34, P = 0.001). Overhydration (OH) (β = 0.33, P = 0.001) and presence of diastolic dysfunction (β = 0.226, P = 0.027) had positive correlations with NT-proBNP. In the subgroup analysis with diastolic dysfunction grade, NT-proBNP increased as the dysfunction grade increased. diastolic dysfunction grade 0: 4177(2637-10391), grade 1: 9736 (5471-21110), grade 2, 3: 24627(16975-44988) Elevation of NT-proBNP above 4058 pg/ml was associated with the presence of diastolic dysfunction (p = 0.001) and Left ventricular hypertrophy (LVH) (p < 0.004). Elevation of NT-proBNP above 1157 pg/ml was associated with the presence of diastolic dysfunction (P < 0.004), LVH (p = 0.001) as well as EF<55% (p = 0.07). The group with lowered dry weight followed up NT-proBNP one month later, compared to the group with no change in dry weight, NT-proBNP showed a tendency to decrease, and the group with no change in dry weight showed a relatively low level of NT-proBNP variability. (-210 (-12899 - 3142) x 330 (10900 - 3858); interquartile range, p = 0.104)

Conclusions: We confirmed that NT-proBNP is associated with volume status as well as heart functions such as diastolic dysfunction, LVH and EF in HD patients.

Heart function according to NT-proBNP level

PO0875
Dysregulation of Fatty Acid Binding Protein and Their Relationship with Inflammatory Biomarkers in ESRD
Emily Bontekoe, Vinod K. Bansal, Fakika Siddiqui, Omer M. Iqbal, Jawed Fareed. Loyola University Health System, Maywood, IL.

Background: End stage renal disease (ESRD) patients are at high risk of cardiovascular disorders and hemostatic complications. Fatty acid binding proteins (FABPs) regulate the transport of fatty acids and other lipophilic mediators such as eicosanoids and retinoids by both intracellular and extracellular mechanisms. While upregulation of FABPs have been reported in ESRD, their relationship with inflammatory biomarkers is not fully understood. Liver fatty acid binding protein (L-FABP) also known as FABP-1 is a 14kDa protein expressed in the liver. This protein is also expressed in tubular kidney cells. Kidney damage and other pathologic conditions result in the marked upregulation of this protein.

Methods: Citrated blood samples from 95 ESRD patients undergoing maintenance hemodialysis were collected prior to hemodialysis. For comparison purposes normal human plasma collected from 50 normal healthy male and female individuals were used. Plasma prepared from these patients and normal individuals was analyzed for FABP-1 and such inflammatory biomarkers as IL-6, TNFa and inflammasomes as using commercially available ELISA methods. All results were compiled and correlation analysis between FABP-1 levels and biomarkers of inflammation was carried out using GraphPad prism software.

Results: The ESRD patients showed a marked increase in FABP levels (106 ng/ml ± 18ng/ml SEM) with a broad range (8 – 974 ng/ml) in comparison to normal (5.1 ± 0.2ng/ml SEM) with a range of (3.4 – 9.2 ng/ml). Marked increases in IL-6, TNFa and inflammation were also noted (2 – 4 fold). FABP-1 showed varying degrees of positive correlation with inflammatory biomarkers.

Conclusions: These studies suggest that plasma levels of FABP-1 is markedly increased (up to 10 fold) in ESRD patients undergoing maintenance hemodialysis. Other biomarkers of inflammation are also upregulated and demonstrate varying degrees of correlation suggesting inter-relationship between FABP-1 and inflammatory processes. These results also suggest that impaired renal function and tubular damage contribute to the marked increase of L-FABP in ESRD patients. Simultaneous measurement of L-FABP with biomarkers of inflammatory responses and kidney damage may be helpful in the risk stratification and prediction of the adverse outcome in ESRD patients.

Funding: Private Foundation Support
Transcapillary Refilling Rate Profile in Hemodialfiltration
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Background: Reaching dry weight in end-stage kidney disease (ESKD) patients is subject to high ultrafiltration rates (UFR) during their hemodialfiltration (HDF) sessions. We seek to profile the transcapillary refill kinetics rate (TRR) during HDF, which we infer to be an important protective factor against intradialytic hypotension (IH).

Methods: We studied 30 patients in HDF scheduled 3 times a week. Absolute blood volume was measured with the dilutional method and plasma volume was calculated based on the patient’s hematocrit. Each session was divided in 18 intervals of 10 minutes each. Overall UFR and UFR at each one were measured to calculate the expected plasma volume. Real plasma volume at the end of each interval was calculated on the basis of the relative blood volume. The difference between the real and the expected plasma volume was the plasma refill volume, which divided by the time of each interval gave us the TRR. The HDF session prescription was determined by the nephrologist in charge of the HDF clinic.

Results: 84 HDF sessions were recorded. Mean age was 44 years (40 to 48), 66% were female. TRR:UFR ratio difference between patients with and without IH was statistically significant (p < 0.001, CI 95%), as well as the UFR-TRR delta (p < 0.001, CI 95%). This ratio achieved stability after 30 minutes. Eight patients (27%) presented an IH episode during HDF, in a total of 9 sessions (10.75%); 8 (89%) occurred in the final hour and 1 (11%) occurred in the first 10 minutes and corresponded to a patient who presented fever and bacteremia.

Conclusions: Both the TRR:UFR ratio and UFR-TRR delta were statistically significant for predicting IH. Understanding each patient’s TRR will help us plan interventions in order to try and optimize it and reduce the risk of IH.

Impact of Hydration Status Measurement by Bioimpedance Analysis (BIA) on Haemodialysis Patients
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Background: Volume status in haemodialysis patients is an important prognostic factor. Overhydration is associated with a higher frequency of mortality while diuresis-induced volume depletion is also an independent mortality risk factor. Clinical indices do not always accurately reflect volume status. Bioimpedance analysis (BIA) is used as a simple, noninvasive method which can measure normovolemic status in haemodialysis patients by measurement of height, weight, and body composition. Fluid overload is calculated by subtracting the normovolemic status from the overhydration status.

Methods: All patients at Queens satellite dialysis unit, Romford, United Kingdom, which has a prevalent population of 106 patients had BIA based assessment of fluid status every 3 months from July 2020 to May 2021 and dry weight adjusted accordingly. Outcomes were noted for blood pressure, overhydration, Interdialytic weight gains, intradialytic hypotension, hospitalisation and mortality.

Results: 121 haemodialysis patients were followed with male to female ratio of 55:46, mean age of 62 (25-87) of whom 46 were diabetics. By end of assessment period, 21 patients had died (13 due to COVID related illness). In July 2020, 31 patients had overhydration of 2 litres or more, which reduced to 20 patients, in May 2021. The number of patients who had underhydration of -1 litre or more remained similar with 12 patients in July 2020 compared to 11 in May 2021 in spite of more aggressive approach to reduction in dry weight. The dialysis population had high turnover due to deaths as well and 2 transfers out of the unit. During the time of study 15 patients were admitted to hospital with features of fluid overload.

Conclusions: Bioimpedence analysis (BIA) is a simple, non invasive tool helpful in assessing fluid status in haemodialysis patients. It is easier to convince a patient about their volume status by providing a machine assessed figure rather than clinical parameters. There was significant improvement in overhydration without increasing the number of deaths in patients. The high mortality in prevalent patients during COVID pandemic highlights the need for continued body composition measurements in a larger population once COVID cases subside to come to a significant conclusion about the impact of BIA in improving patient outcomes including effect on residual renal function.

Association of Different Definitions of Intradialytic Hypertension with Long-Term Mortality in Hemodialysis
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Background: Hypertension is common in patients receiving maintenance hemodialysis (HD). A subset of patients experience increases in systolic blood pressure (SBP) from pre- to post-HD (intradialytic hypertension). This phenomenon is known to be associated with adverse short and long-term outcomes, but there is little consensus on an evidence-based definition.

Methods: In a retrospective cohort of 3,198 HD participants, unadjusted and adjusted Cox proportional hazards models were fit to examine the association of various definitions of intradialytic hypertension (≥30% of baseline sessions with an increase in pre- to post-HD SBP of 1) ≥ ± 10 mmHg [Hyper0]; 2) ± 20 mmHg [Hyper10], or 3) ≥ 20 mmHg increase [Hyper20]) with all-cause mortality. Interaction terms were used to assess for effect modification according to pre-specified demographic (age, sex), HD-related (pre-HD SBP, ultrafiltration rate), and comorbid disease variables (diabetes, heart failure, and peripheral vascular disease [PVD]).

Results: At baseline, mean age was 62 ± 15 years, 57% were male, and 14% were Black. Average change in BP from pre- to post-HD was 13 ± 16 mmHg (median 12 [3 to 22] mmHg). During the baseline period, 47% of individuals met the Hyper0 definition and were at a 29% (HR 1.29; 95%CI 1.05 to 1.62) higher adjusted risk of death, compared with participants with no SBP increase. Hyper10 was present in 21.2% and associated with a 21% higher adjusted risk of death (HR 1.21; 95%CI 0.96 to 1.51). Hyper20 was present in 6.8% and associated with a 5% higher risk of death (HR 1.05; 95%CI 0.76 to 1.46). There was evidence for effect modification by age and PVD (Interaction=0.02 for both), with a higher risk of death in those aged 45-70 years and those without PVD. Funding: NIDDK Support.
had more pericardial effusions (12.5% vs 2.3% p = 0.048) and more GIB (12.5% vs 2.2% p = 0.046) (Table 1). There were no differences in in-hospital mortality, hospital length of stay (LOS), ICU LOS, and sternal wound infections between groups across the different surgeries. 16 PD patients were converted to HD post-surgery, intent to treat analysis was applied for these patients.

**Conclusions:** In patients on maintenance dialysis, patients who underwent CABG, VS, and combined surgery had similar outcomes. PD patients appeared to experience more GIB and pericardial effusions requiring intervention in the CABG group.

**Table 1**

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**PO0881**

**Prevalence and Risk Factors for Development of Cardiac Arrhythmias and Electrocardiographic Abnormalities in Hemodialysis Patients: A Single-Center Experience in Mexico.**

**Andrea San-German Morales, 1 Pedro A. Escamilla Galindo, 2 Armando Castillo Garcia, 3 Paulina Paniagua, 4 Juan M. Ardavin Ituarte, 2 Mario Jimenez Hernandez 1, 2 Universidad de las Americas Puebla, Cholula, Mexico; 3 Medica Santa Carmen, Puebla, Mexico.**

**Background:** Mexico is among the countries with the highest number of patients on kidney replacement therapy (RRT). Despite this, the incidence and prevalence of CKD in Mexico is unknown, due to the lack of a national registry as a result we do not know risk factors associated to this population. Electrocardiographic abnormalities or arrhythmias are among the most frequent cardiovascular pathologies, being the first cause of death during the first month in RRT. That is why the present study aims to identify the prevalence of arrhythmias in a group of Mexican patients on hemodialysis as well as their associated risk factors.

**Methods:** A non-experimental, observational, descriptive, and cross-sectional study was carried out in the period from March to July 2020 with Mexican patients older than 18 years in maintained hemodialysis. The electrocardiograms and blood test analysis were taken on the day of hemodialysis therapy.

**Results:** The mean age of the population was 42.37 years, 57% were male. Arrhythmias were found in 50 patients (41.67%), the prevalence of arrhythmias found was bundle branch block (17.50%), sinus tachycardia (12.50%), sinus bradycardia (7.50%), atrial fibrillation (2.50%), extrasystoles (1.67%). A significant difference in mean ages was found between patients with (47.14) and without arrhythmia (38.97) (P = 0.041). A history of heart disease (OR 7.54 95% CI 1.05-184.7), and the diagnosis of chronic renal failure secondary to diabetic nephropathy (OR 2.5459 95% CI 1.1026-5.8785) were identified as risk factors. The diagnosis of chronic renal failure secondary to arterial hypertension was not related as risk factor (p=0.86). No laboratory study was identified as a risk or protective factor for the development of arrhythmia either the vascular access type.

**Conclusions:** The studied population presented similar characteristics to the described previously, a high prevalence of electrocardiographic abnormalities was identified, laboratory studies were not related to the presence of arrhythmias. History of heart disease and kidney disease secondary to diabetic nephropathy were associated as a risk factors, while the presence of arterial hypertension was not identified as risk factor.
PO0883

Knowledge and Practice of Incremental Dialysis: A Survey of Canadian Nephrologists


Background: Incremental hemodialysis, a strategy to individualize dialysis prescription at initiation, is being linked to enhanced quality of life and acceptability by patients and decreased health care costs. We aimed to explore knowledge and practice pattern regarding facility-based incremental hemodialysis in Canada.

Methods: A web-based survey of nephrologists, elicited current incremental hemodialysis (HD) prescribing practices, clinical and patient factors used to determine suitability for treatment, and potential barriers to implementation. The survey was circulated over a period of six weeks (September 21, 2020 and October 30, 2020).

Results: The overall response rates 35% (243/691 nephrologists surveyed). Majority (66/111, 59%) of respondents prescribed incremental HD using an individualized approach at the discretion of the nephrologist. Most centers (200/203, 98%) did not report policy or guidance for implementation. Residual urine output was identified as the most important factor for eligibility (112/172, 65%), electrolyte stability (76/172,44%) and existing patient goals of care (69/117, 46%). The majority of nephrologists agreed that dialysis prescriptions are dynamic and should take residual kidney function into consideration; however, 74% of nephrologists did not think there was strong evidence supporting incremental dialysis. Potential barriers identified were patient safety, logistics of scheduling, limited evidence, and acceptance of dose escalation. Despite these barriers, 82% of participants felt that this facility-based incremental dialysis is feasible with their current resources and 78% agreed that with specific exclusion and inclusion criteria, incremental dialysis is a safe option.

Conclusions: Incremental hemodialysis is commonly practiced amongst Canadian nephrologists despite a lack of formal criteria for initiation and treatment escalation. This highlights a need for research to guide policy and practice for incremental hemodialysis in Canada.

PO0884

Thrice vs. Twice Weekly Hemodialysis in a Rural Community Center

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Background: Converting stable ESRD patients from thrice to twice weekly HD sessions is a well-accepted strategy in the dialysis community. Present study aimed to determine the feasibility, practicality and impact of this approach at the discretion of the nephrologist. Most centers (200/203, 98%) did not report policy or guidance for implementation. Residual urine output was identified as the most important factor for eligibility (112/172, 65%), electrolyte stability (76/172,44%) and existing patient goals of care (69/117, 46%). The majority of nephrologists agreed that dialysis prescriptions are dynamic and should take residual kidney function into consideration; however, 74% of nephrologists did not think there was strong evidence supporting incremental dialysis. Potential barriers identified were patient safety, logistics of scheduling, limited evidence, and acceptance of dose escalation. Despite these barriers, 82% of participants felt that this facility-based incremental dialysis is feasible with their current resources and 78% agreed that with specific exclusion and inclusion criteria, incremental dialysis is a safe option.

Conclusions: Incremental hemodialysis is commonly practiced amongst Canadian nephrologists despite a lack of formal criteria for initiation and treatment escalation. This highlights a need for research to guide policy and practice for incremental hemodialysis in Canada.

PO0885

Impact of the Ratio of Monocyte to High-Density Lipoprotein Cholesterol on Cardiovascular Outcome in Incident Dialysis Patients


Background: Monocyte count to high-density liprotein ratio (MHR) is a well known risk factor of cardiovascular event-free survival rate between the low MHR group and the high MHR group. The secondary outcome included all-cause mortality, overall CV mortality and possibility of MHR as an independent risk factor for CV complication.

Methods: The medical records of 719 ESKD patients who started maintenance dialysis between January 2006 and July 2017 were reviewed. Patients were divided into low MHR and high MHR groups based on the median MHR value.

Results: Overall CV event was 130 cases, 55 in the low MHR group and 75 in the high MHR group, respectively. The CV event-free survival rate was significantly lower in the high MHR group compared to the low MHR group (47.6% vs. 57.5%, P = 0.017). Of the 577 enrolled patients, there was no statistical difference in all-cause mortality between the two groups during a mean follow-up of 3.2 years (P = 0.371). Overall CV mortality rate was also comparable between the two groups (~0.615). In multivariate Cox regression analysis, high MHR was an independent predictor for CV events (HR 1.463, 95% CI, 1.019 – 2.102, P < 0.039) even after adjustment for age, smoking, diabetes, body mass index, C-reactive protein, and previous CV disease.

Conclusions: In conclusion, high MHR at the time of dialysis initiation in the incident ESKD patients may be a simple and useful method for predicting development of CV complication.

PO0886

Differences in Clinical Characteristics and Outcomes Between Hemodialysis-Dependent and Non-Hemodialysis-Dependent Patients with Gram-Negative Bacteremia

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Background: Gram-negative bacteremia (GNB) is a common and potentially lethal infection among hemodialysis (HD)-dependent patients. The determinants of clinical outcomes in HD-dependent patients with GNB are incompletely understood. We compared clinical characteristics and outcomes between HD- and non-HD-dependent patients with GNB in a large cohort of hospitalized patients and subsequently examined associations between specific characteristics and all-cause mortality among HD-dependent patients.

Methods: Hospitalized, non-neutropenic adults with GNB were prospectively enrolled from Jan 1, 2002 to July 1, 2015. Clinical characteristics and outcome data were collected. Differences between HD- and non-HD-dependent patients were estimated using means/standard deviations or counts/percentages with statistical significance evaluated with independent sample T-tests or Pearson’s chi-squared test. Associations between clinical characteristics and outcomes were estimated using logistic regression.

Results: Among 1,827 unique participants, 180 were HD-dependent (9.9%). Compared to non-HD-dependent patients, HD-dependent patients were younger (58.6 vs 61.0 years, p=0.05) and more likely to be Black (55.6% vs 26.4%, p<0.001), to have diabetes (56.1% vs 32.1%, p<0.001), and to die prior to hospital discharge (28.9% vs
19.9%, p=0.01). Among HD-dependent patients, having a higher total APACHE II score (Odds ratio [OR] 1.15, Confidence Interval [CI] 1.08-1.23), non-central venous access, source of infection (OR 8.00, CI 2.71-23.60) or hospital-acquired infection (OR 4.46, CI 2.19-9.09) were associated with in-house mortality, while Black race (OR 0.31, CI 0.16-0.63) was inversely associated with mortality.

**Results:** A total of 24 clinical characteristics and outcomes differed significantly between HD- and non-HD-dependent patients with GNB. Mortality among HD-dependent patients may be partially explained by source of infection, site of acquisition, and severity of illness at time of infection. The association between race and patient outcome requires further study.

**Funding:** NIDDK Support, Other NIH Support - K24-AI093969

PO0887

**Predictors of Hyperkalemia Among Chronic Hemodialysis Patients Transferred to the Emergency Department**

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**Background:** Chronic hemodialysis (HD) patients often present to the emergency department (ED) with hyperkalemia, which in turn, is associated with morbidity and mortality. In this study we sought to identify pre-hospital predictors of hyperkalemia in patients transported to the ED via ambulance (ambulance-ED).

**Methods:** We analyzed all ambulance-ED transports in a cohort of chronic hemodialysis patients from 2014-2018 (using a province-wide emergency medical services database). The outcome was severe hyperkalemia using the first blood draw after ambulance-ED transport defined as ≥6 mmol/L. Characteristics of interest included vital signs prior to transport, days from last dialysis and prehospital electrocardiograms (ECGs) interpreted by paramedics prior to transport. The association between prehospital factors and hyperkalemia was analyzed using adjusted logistic regression.

**Results:** Of 370 chronic HD patients transferred by ambulance-ED, 16% had severe hyperkalemia (≥6 mmol/L). Compared to non-hyperkalemia patients, hyperkalemic patients were more likely to have pre-dialysis vital signs consistent with hypotension (45% vs 19%, p<0.001), hypoxia (34% vs 21%, p=0.001), and a slower heart rate (37% vs 23%, p=0.001), and more likely to be transferred to the ED during the daytime (70% vs 55%, p=0.01). Patients with severe hyperkalemia had a greater emergency department (ED) length of stay (5.2 hours vs 3.7 hours, p=0.001), and were more likely to be re-transported to ambulance-ED (24% vs 14%, p=0.01) or admitted to hospital (73% vs 61%, p=0.001) compared to non-hyperkalemia patients. In an adjusted parsimonious model (Table 1, N=609), age, dialysis vintage, bradycardia and days from last dialysis were associated with severe hyperkalemia. Among those with prehospital ECGs (N=377), presence of a prehospital ECG abnormality (i.e. peaked t-waves and/or first-degree atrioventricular block) was strongly associated with ED hyperkalemia (odds ratio 6.64, 95% confidence interval 2.31-19.12). Overall, 45% of hyperkalemic patients versus 24% of non-hyperkalemic patients required re-transport to another hospital to facilitate dialysis in a monitored setting after initial presentation.

**Conclusions:** A total of 24 clinical characteristics and outcomes had 94% in univariate logistic regression analysis

**Adjusted predictors of severe hyperkalemia after transport to the emergency department (n=609)*

| Age at ED (each year) | 0.07 | 0.095-0.009 | 0.009 |
| Male sex | 1.34 | 0.61-2.15 | 0.981 |
| Hemodialysis vintage (each year) | 1.38 | 0.18-1.21 | 0.835 |
| Days from last HD relative to ED transport | | |
| Same day but prior to ED transport | | |
| Two | 1.11 | 1.08-24.04 | 0.940 |
| Three or more | 1.89 | 4.58-69.49 | 0.018 |
| Heart rate prior to ED transport | | |
| 60-90 (best vs) | | |
| 90-120 (best vs) | | |
| Heart rate (best vs) | | |
| Heart rate (best vs) | | |
| OR: Odds ratio; CI: confidence intervals; HD: hemodialysis; ED: emergency department

*Includes variables had a >0.40 in univariate logistic regression analysis

**PO0889**

**Efficacy of Patiromer and Sodium Polystyrene Sulfonate on Potassium Levels in Chronic Hemodialysis Patients**

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**Background:** While hyperkalemia is frequent in haemodialysis (HD) patients and is associated with increased mortality, evidences regarding treatment options are limited. We compared the effect of sodium polystyrene sulfonate (SPS) and patiromer on potassium control in this population.

**Methods:** We screened 180 prevalent chronic HD patients, and included 52 patients with pre-HD potassium >5.1 mmol/L without potassium binder in a cross-over trial comparing on non-dialysis days SPS 15 g before each meal to patiromer 16.8 g once a day. Treatment duration was four weeks with a 2-week intermediate wash-out period. Treatment attribution order was randomized. Pre-HD potassium level was measured at each dialysis session and tolerability assessed on a semi-quantitative scale from 0 to 10. Results: 45 patients terminated the study without missing values on considered variables. Mean age was 66.3 +/- 19.2 with 74 % male and 44% diabetic patients. Mean pre-dialysis potassium were 4.5 +/- 0.7 mmol/L and 5.0 +/- 0.5 mmol/L under SPS and patiromer respectively. In mixed linear regression, treatment with SPS was associated with a decrease of 0.47 mmol/L in mean weekly pre-HD potassium compared to patiromer (p=0.001). Tolerability score was 6.0 +/- 2.4 and 7.0 +/- 1.8 under SPS and patiromer respectively (p=0.001). Conclusion: In chronic HD patients, SPS 15 g before each meal on non-dialysis days resulted in lower pre-dialysis potassium values as compared to patiromer 16.8 g once a day, although tolerability was poorer. Those findings as well as dose titration need to be tested in larger randomized trials.

**Funding:** Clinical Revenue Support

PO0890

**Associations of Serum and Dialysate Potassium Concentrations with Incident Atrial Fibrillation in Older US Persons Initiating Hemodialysis for Kidney Failure**

Austin Hu,1 Sai Liu,1 Maria E. Montez-Rath,1 Pascale Hairallahl,2 Jingbo Niu,2 Tara I. Chang,1 Wolfgang C. Winkelmaeyer.1 Stanford University School of Medicine, Stanford, CA; Baylor College of Medicine, Houston, TX.

**Background:** Atrial fibrillation (AF) is the most common arrhythmia and affects more than a third of U.S. patients with kidney failure on hemodialysis (HD). Hyperkalemia is a common concern in the HD population and been associated with higher mortality, especially sudden death. However, little is known about the associations of serum potassium (S-K) and dialysate potassium (D-K) concentrations with incident AF in persons on HD.

**Methods:** We used health records data of a large dialysis provider merged with the US Renal Data System (2006-11). We identified persons ages 67+ years initiating HD who had ≥2 years of prior Medicare coverage and not been diagnosed with AF by day 120 after start of HD. Subsequent 30 day periods were created during which S-K measurements were averaged; the most recent D-K in the preceding 30 day window was also recorded. Demographic, comorbidity, and health utilization variables were defined as other laboratory/biometric characteristics. The outcome, newly-diagnosed AF during the subsequent 30 days, was recorded from claims. This process was repeated after frame-shifting all measurements by 30 day increments. Cox regression was used to estimate hazard ratios.
Results: We studied 15,190 persons on HD without prior AF diagnosis; average age was 76 yrs, 49% were male; 69% were white, 26% black, and 8% Hispanic. At baseline, 7137 persons had a S-K+ ≥4.5 and 6988 ≤4.5 mEq/L. With the exception of race and ethnicity, all other characteristics, including D-K+, which was 2 mEq/L in 52% and 3 mEq/L in 34%, were balanced between groups. During a mean follow-up of 327 days the overall incidence of AF was 13/100 person-years. S-K+ and D-K+ were positively correlated, but not with higher S-K+ concentrations unless extreme values >6.5 mEq/L were reached. D-K+ of 3 mEq/L vs. 2 mEq/L, was associated with 14% (95% CI: 5-24%) lower adjusted rates of AF. No interaction between S-K+ and D-K+ was observed.

Conclusions: Hypokalemia was strongly and independently associated with incident AF whereas hyperkalemia was not. However, choice of D-K+ of 2 mEq/L vs. 3 mEq/L did not associate with higher AF rates, independent of S-K+ and other measured characteristics.

Funding: NIDDK Support

PO0891
Serum Potassium Changes in US Veterans Receiving Patiromer with Dialysis-Dependent ESKD and Hyperkalemia
Christopher Csaba1, Elvira O. Gosmanova,2 Steven D. Woods,3 Christopher G. Rowan,4 Jared Hansen,5 Brian C. Sauer. The University of Tennessee Health Science Center, Memphis, TN; 1Albert Medical College, Albany, NY; 2Vifor Pharma, Inc., Redwood City, CA; 3COHRDATA, San Clemente, CA; 4Salt Lake City VA Medical Center (IDEAS), Salt Lake City, UT.

Background: Patiromer is a sodium-free, non-absorbed, potassium (K+) binding polymer approved for the treatment of hyperkalemia (HK). This retrospective cohort study aimed to describe serum K+ changes in Veterans with HK and end-stage kidney disease (ESKD) receiving dialysis who initiated patiromer.

Methods: Serum K+ concentrations were evaluated pre- and post-patiromer initiation using the National VA Corporate Data Warehouse (1/1–6/31/18). Changes in mean serum K+ concentration were compared at 1, 3, and 6 months following first patiromer dispensing (index date) using the paired t-test (pre K+ versus post K+). All patients had a baseline K+ ≥5.1 mEq/L and ESKD. Patients with continuous exposure to patiromer were analyzed. Follow-up began on the index date and ended at first censoring event (discontinuation or switch of index K+ binder, death, end of follow-up, or 6 months post-index).

Results: 98 patients with ESKD requiring dialysis and HK initiated patiromer. Patient characteristics at baseline were median age 66 years, African-American race 39%, diabetes 71%, heart failure 40%, and mean K+ value of 6.1 mEq/L (standard deviation = 0.7). The initial dose of patiromer was 8.4 g in 96% of patients with few observed increases in unit dose during the follow-up period. Following patiromer initiation, statistically significant reductions in serum K+ concentration were observed at 1 month (~1.24 mEq/L), 3 months (~1.15 mEq/L), and 6 months (~1.36 mEq/L, Figure). No significant change was observed from baseline to 12 months of patiromer use. Patients with HK, as squarer, was associated with clinically relevant reductions in serum K+ concentrations at all study time points. These findings warrant additional investigation in a larger dialysis cohort with HK.

Funding: Commercial Support - Vifor Pharma, Inc.

PO0892
Hyperkalemia: Medical Management vs. Hemodialysis
Joseph A. Gotesman, Mario V. DeVita. Lenox Hill Hospital, New York, NY.

Background: Hyperkalemia is a life-threatening electrolyte disorder for which there exists a paucity of data regarding benefit of urgent hemodialysis over medical management. We hypothesized there would be no difference in potassium levels among hyperkalemic patients who received only medical management compared to those who received hemodialysis, with or without hemodialysis.

PO0893
Metabolic Alkalosis in Hemodialysis Patients
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Background: Hemodialysis (HD) typically employs a high dialysate alkali concentration to counteract interdialytic acid production. Since acid production varies due to the amount and type of protein consumed, some patients may remain alkalotic throughout the interdialytic period and be more alkalotic during HD. This could have adverse effects including arrhythmias, hypotension, hyperventilation, and vascular calculation but dialysate alkali is rarely adjusted. Pre-HD alkalosis is usually ascribed to chronic illness and poor nutrition, but this has not been carefully examined.

Methods: We conducted a retrospective case-control study of all in-center HD patients from 2010 - 2020 at 4 outpatient HD units using citrate-containing dialysate (34.6 meq/L HCO₃, 0.4 meq/L acetate, 2.4 meq/L citrate; citrasate, Fresenius). Interaldialytic alkalosis was defined as pre-HD serum [HCO₃] ≥26 in ≥ 7 months of any 12-month period. Patients with persistent alkalosis defined as interdialytic alkalosis in every subsequent 12-month period. Patients with serum [HCO₃] 19-23 in ≥ 7 months of every 12-month period constituted the control cohort.

Results: Of 1271 patients with at least 12 months of HD, 444 met the alkalosis criteria for at least one 12-month period and 73 had persistent alkalosis. 189 patients met the control criteria for every 12-month period. Patients with persistent alkalosis were older (66 vs 55 years, p<0.001) and weighed less (69 vs 82 kg, p=0.003), but the prevalence of comorbidities including cardiovascular disease, neoplasia, and diabetes was not increased. HD dose (kT/V) was greater (1.47 vs 1.37, p<0.001), protein catabolic rate was lower (0.85 vs 0.96 g/kg/day, p<0.001), and interdialytic weight gain was less (1.62 vs 2.28 kg, p<0.001). Despite significant weight loss over time (7 ± 13 vs 0 ± 9 kg, p<0.001), mortality was not increased when adjusted for age, serum albumin was only slightly lower (3.71 vs 3.80 g/dl, p=0.05), and cause of primary morbidity/chronic illness such as serum cholesterol and hemoglobin did not differ from control patients.

Conclusions: Persistent interdialytic alkalosis was common in this HD population and persistent alkalosis was not rare (~5%). Alkalosis appeared to result from a greater dialysis dose and lower protein intake but not chronic illness. Further studies are needed to determine whether this alkalosis is detrimental and adjustment of dialysate [HCO₃] is indicated.

PO0894
Metabolic Alkalosis in Hemodialysis Patients: Worse Outcomes

Background: The ideal serum bicarbonate levels in prevalent hemodialysis (HD) patients is still debatable. Metabolic alkalosis in these patients has been associated with increased morbimortality. The aim of this study was to evaluate the association between serum bicarbonate and nutritional and cardiovascular risk markers, hospitalizations and mortality.

Methods: This was a single-center, retrospective study, of a cohort of 158 in-center HD patients, with a duration of 24 months. Serum bicarbonate levels were evaluated predialysis every 3 months. Body Composition Monitor was used to assess nutritional and biomarkers. Electrocardiogram and echocardiography data were obtained to calculate the QTc interval and the left ventricular mass index, respectively. Vascular calcifications were assessed using the Adragao score (SVCS).

Results: Mean age of the population was 69±12.6, 73% were male and 45% had diabetes. Mean HD vintage was 69 months (IQR: 65 months). Mean body mass was 23.5±1.57 mEq/L. There was no inverse association between serum bicarbonate and body mass index (r=-0.22, p=0.006), lean tissue index (r=-0.35, p<0.001), hemoglobin (r=-0.19, p=0.016), albumin (r=-0.30, p=0.001), phosphorus (r=-0.33, p<0.001) and nPCR.
Dysfunction. The proinflammatory response in COVID-19 produces dysfunction and understood. Reported cases of PRES have been linked with hypertension, autoimmune Nicardipine drip was weaned, and he was transitioned to oral blood pressure medications. Patient was found to be positive for COVID-19 and did not receive treatment for it as his to 166/105 mmHg. His vision restored fully without further episodes of vision loss. He was started on Nicardipine drip in the ICU with subsequent decrease in blood pressure of all-cause mortality (p<0.004) in a model adjusted for age, dialysis vintage and the presence of diabetes.

Conclusions: In this population, higher serum bicarbonate was associated with a worse nutritional status and a higher cardiovascular risk, assessed by Adragão score. There was an association with an increased number of infection-related hospitalizations and mortality, as well as higher all-cause mortality. Serum bicarbonate levels ≥24.5 mEq/L were associated with lower survival at 24 months. Prospective studies are needed to determine the ideal serum bicarbonate levels in HD patients.

PO0895
The Use of Caffeine to Treat Intradialytic Hypotension
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Introduction: Intradialytic hypotension (IDH) affects over 10% of individuals on hemodialysis (HD) and can cause long-term multisystemic ischemic damage. One proposed mechanism for IDH is the accumulation of local adenosine causing vasodilation. Agents such as midodrine and caffeine counter these vasodilatory effects. Herein we present a case of IDH where the ingestion of caffeine prior to HD sessions significantly reduced the severity of IDH.

Case Description: A 77-year-old female with CKD-5, longstanding hypertension, and type 2 diabetes mellitus was admitted for initiation of HD. During her 1st HD session, she experienced IDH with a sudden drop in her systolic blood pressure (SBP) from the 193 to 113, accompanied by loss of consciousness and convulsions of the bilateral upper extremities. She recovered consciousness without a postictal state and no significant changes on ECG. Echocardiography ruled out pericardial effusion. On subsequent HD sessions, the patient continued to experience IDH with average decreases of over 100mmHg in her SBP. Initial management by lowering blood flow rate, lowering dialysate temperature, and holding the patient’s pre-dialysis antihypertensive regimen had only a mild effect in preventing IDH. Given previous studies showing the efficacy of 250 mg caffeine capsules in preventing IDH, we tested the effect of caffeine on this patient’s IDH. 30 minutes prior to her next inpatient HD session, we administered 10 oz of coffee (150 mg of caffeine). Her drop in SBP during that session was markedly reduced from 187 to 149.

Discussion: Non-pharmacological measures to prevent IDH have been previously implemented but lack well-powered clinical trial evidence. Using coffee as a vehicle for caffeine administration was an effective preventive measure for IDH in our patient. We hypothesize that this effect is adenosine inhibition mediated. Adenosine is released by cells undergoing localized ischemia during HD, causing vasodilation. Studies show an increase of serum adenosine during IDH. Caffeine is a non-selective adenosine receptor antagonist, and can prevent sudden vasodilatation during dialysis. Thus, coffee may be an effective alternative to midodrine for the prevention of IDH. In conclusion, coffee provided a readily available, inexpensive, patient-centered, non-pharmacological measure to reduce IDH while also decreasing the risk of polypharmacy.

PO0896
A Case of Posterior Reversible Encephalopathy Syndrome (PRES) in an ESKD Patient with COVID-19
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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological syndrome first reported in 1996 which describes the presence of a wide range of neurological symptoms, and posterior brain white matter edema on imaging studies which may be reversible. The clinical presentation is characterized by headaches, altered consciousness, visual disturbances and seizures; hypertension is frequent, although not invariable.

Case Description: A 37-year-old male with past medical history of hypertension and unknown etiology hypertension, being on hemodialysis with shortness of breath, occipital headache, altered consciousness, visual disturbances and seizures; hypertension is frequent, although not invariable. On admission, he was afibrile with a blood pressure of 274/147 mmHg, RR of 16, HR 98 bpm and oxygen saturation of 89% on room air. Due to acute vision loss, a stroke alert was initiated. A head CT scan showed subcortical hypodensities in the bilateral occipital lobes consistent with PRES. He was started on Nicardipine drip in the ICU with subsequent decrease in blood pressure to 166/105 mmHg. His vision restored fully without further episodes of vision loss. Patient was found to be positive for COVID-19 and did not receive treatment for it as his shortness of breath and hypertension was resolved. The patient received maintenance dialysis using Nicardipine drip was weaned, and he was transitioned to oral blood pressure medications.

Discussion: The relationship between kidney disease and PRES is not fully understood. Reported cases of PRES have been linked with hypertension, autoimmune disorders, and immunosuppressive states, common conditions in ESKD. The pathophysiology of PRES appears to be related to cerebral blood flow dysregulation and endothelial cell dysfunction. The proinflammatory response in COVID-19 produces dysfunction and death of endothelial cells which may increase vascular permeability, promoting the cerebral edema seen in PRES. The estimated prevalence of PRES in COVID-19 patients is between 1-4%. Reports of PRES in ESKD are rare. PRES may not be readily recognized given the heterogeneity of presentation. Therefore, high index of suspicion is needed in the ESKD population.

PO0897
Eye Pain During Hemodialysis: Ocular Dialysis Disequilibrium? Sarah Abbass Massali,1 Monika Aggarwal (Gupta).3 Virginia Commonwealth University Health System, VA; 4 Victoria Richmond Medical Center, Richmond, VA.

Introduction: Changes in Intraocular pressure (IOP) during hemodialysis (HD) are underrecognized. We report a case of increased IOP during HD, successfully treated with adjustments to dialysis prescription.

Case Description: 39-year-old African American man with End Stage Renal Disease (ESRD) secondary to diabetic nephropathy on HD since 2017, presented with exorucing right eye pain during HD for 2 weeks. He described increasing right eye pain during HD, requiring early termination of dialysis after 3 hours. He has known right eye glaucoma with no vision. He was on atropine sulfate, prednisolone acetate, latanoprost, dorzolamide/timolol, and brimonidine tartrate eye drops. IOP in right eye was 63 and 80 mm of Hg, before and after hemodialysis, respectively. Left eye IOP were < 20 mm of HG and did not change significantly with dialysis. Due to concerns for ocular dialysis disequilibrium; blood flow rate, dialysate flow rate, dialysate temperature, and dialysate sodium were changed to 400 ml/minute from 450 ml/minute, 500 ml/minute from 800 ml/minute, 35.6°C from 37°C, and 145 mEq/L from 140 mEq/L, respectively. Subsequently to changes to dialysis prescription, patient was able to complete dialysis with no worsening of right eye pain and IOP (62 and 64 mm of Hg before and after dialysis, respectively).

Discussion: Increase in IOP during HD is thought be due to rapid decline in plasma osmolality relative to aqueous humor, creating an osmotic gradient that causes movement of water into the eye. Patients with normal eye outflow have minimal rise in IOP as aqueous humor is drained simultaneously. However, patients with glaucoma are not able to drain excess water, causing increase in IOP and eye pain. Older age, diabetes mellitus, and African-American race are risk factors for ESRD and Glaucoma. Early recognition of ocular dialysis syndrome can allow for safe delivery of dialysis in patients with glaucoma. While acetazolamide is an effective treatment for raised IOP, it’s efficacy and safety in ESRD remains unknown. Similarly role of Mannitol in mitigation of ocular dialysis disequilibrium is unclear. Our patient had resolution of ocular dialysis disequilibrium with decrease in blood and dialysate flow rates, increase in dialysate sodium, and decrease in dialysate temperature. Increase in ultrafiltration may also reduce risk of ocular dialysis disequilibrium by raising extracellular oncotic pressure.

PO0898
The Association of Interdialytic Weight Gain in Long Intervals with Residual Renal Function Decline
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Background: Preservation of residual renal function (RRF) in dialysis patients is important for better prognosis. The effect of interdialytic weight gain (IDWGL) on change of RRF has not been investigated well. We examined the association of IDWGL in long intervals (i.e. 2-day breaks between dialysis treatments) with rapid decline of RRF.

Methods: This retrospective cohort study included 6425 patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between seven categories of IDWGL in long intervals (IDWGL) and rapid decline of RRF using logistic regression model. Rapid decline of RRF was defined as the percent decline in renal urea clearance (KRU) greater than the median value of the cohort in the first year after dialysis initiation. Seven categories of IDWGL were as follows: 0<1%, 1~2%, 2~3%, 3~4%, 4~5%, 5~6%, ≥6%. We also examined continuous associations between IDWGL and rapid decline of RRF using restricted cubic spline analysis.

Results: Higher categories of IDWGL were associated with increased risk of rapid decline of RRF. The odds ratios (95% confidence intervals) of rapid decline of RRF for 3~4%, 4~5%, 5~6%, and ≥6% were 1.04 (0.90-1.20), 1.31 (1.09-1.56), 1.19 (0.94-1.51), and 1.30 (1.14-1.97) (Reference: 2~3%) (Figure a). The restricted cubic spline analysis showed that risk of rapid decline of RRF increased when IDWGL exceeded 2% (Figure b).

Conclusions: Our results showed higher IDWGL was associated with higher risk of rapid decline of RRF. IDWGL exceeded 2%, especially ≥4%, seems to be thresholds for higher risk of RRF decline.
Prevalence of Anti-Erythropoietin Antibodies in Patients with ESRD on Regular Hemodialysis: A Single-Centre Experience
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Background: Recombinant human erythropoietin (rHuEPO) is a glycoprotein that acts as a biological substitute for the endogenous substance used to treat anaemia in individuals with end-stage renal failure. Patients with rHuEPO resistance have been described, requiring higher and higher dosages of the drug to maintain an appropriate haemoglobin level. These antibodies probably cross react with the patient’s endogenous EPO and lead to anaemia that can be more severe than even before the onset of EPO therapy. The prevalence of anti-erythropoietin antibodies in renal patients who respond poorly to erythropoietin is unknown.

Methods: We screened 262 patients who were on maintenance haemodialysis and excluded patients who were malnourished and had chronic liver disease, hypothyroidism, ongoing active autoimmune disease, active infection, on steroid therapy, with bleeding or hemolysis and elderly. 96 ISRD patients who were on recombinant human erythropoietin > 6 months and haemoglobin < 10 g/dL were included. Serum anti-EPO antibodies were detected by enzyme-linked immunosorbant assay technique. All patients were subjected to full history taking and clinical examination. Complete blood count, reticulocyte count, serum creatinine, blood urea, serum albumin, serum ferritin, and haematocrit markers were performed for all patients.

Results: Results showed that 26 patients (27.08%) had the anti-EPO antibodies in their blood, while 70 patients (72.91%) did not have the circulating antibodies. The mean hemoglobin (Hb) level was significantly lower in the antibody positive group (8.4 g/dL ± 1.52) than in the antibody negative group (9.68 g/dL ± 1.14) (P = 0.000). The dose of EPO administered in both studied groups were significantly different. Logistic regression analysis also revealed that gender or age were not associated with any significant variation of serum antibody level. High levels of serum antibodies to EPO are a risk factor for EPO resistance.

Conclusions: Many anaemic ISRD patients treated with recombinant human erythropoietin have a low-affinity immune response to the recombinant protein that is readily detected. Antibodies to rHuEPO were shown to be greater in patients who received high EPO weekly dose. More research into anaemia management protocols in ISRD patients with positive anti-EPO antibodies is needed.

Ocular Dys-equilibrium with Eye Pain During Hemodialysis

Introduction: Eye complications may occur in ESRD patients with glaucoma. Hemodialysis (HD) may lower plasma osmolality at a faster rate than changes in ocular osmolality can adapt. Here we are presenting two cases of ESRD patients who repeatedly develop eye pain only during HD.

Case Description: A 54 y/o Hispanic male with ESRD, right eye blindness & glaucoma who developed right eye pain only during dialysis treatments. The maintenance HD prescription was with duration of 4.5 hr, blood flow rate (BFR) 450mL/min, dialysate flow 800 mL/min, Sodium (Na) 138 mmol/L, Calcium 2.7 mmol/L, Potassium 4.3 mmol/L, Calcium 107 mEq/L, CO2 30mmHg, & an average 2L fluid removal per HD. His BP was 130/140mmHg 80-90 mmHg. In response to the eye symptoms, the BFR was reduced to 350 mL/min & time was increased to 4.5 hr. This change gave the patient initial relief from intradialytic eye pain. Ophthalmologist was able to perform a surgical procedure which would eliminate the intradialytic eye pain. The 2nd case was a 64 y/o AA female with ESRD and glaucoma who developed recurrent left eye pain with headaches only during HD. She went to her Ophthalmologist who renewed her glaucoma medications. This relieved her eye symptoms, and normalized her intradialytic pressure off of dialysis. By taking her eye medications, she no longer developed eye pain or headaches during HD.

Discussion: Glaucoma is an ocular disorder where there is an increased IOP most commonly >22mmHg, this elevated pressure can cause blinding optic neuropathy. The current hypothesis for the rise of IOP during HD is related to an osmotic disequilibrium between the plasma & IO fluid, where the IO fluid is slightly hypertonic compared to plasma. Several medical therapies have been reported to mitigate the IOP increase during HD, such as the use of daily acetazolamide, mannitol infusion or 20% hyperosmolar glucose solution, or modified dialysis parameters with colloid infusion to raise plasma tonicity and decrease fluid shift during HD. However, these maneuvers have not been proven to relieve ocular symptoms. In general, use of higher dialysate Na conc. at hemodialysis are not considered a long term solution to intradialytic ocular hypertension, due to the tendency for increased fluid intake between HDs. Lower BFR with longer duration of hemodialysis treatments has been beneficial in some cases.

Caffeine Overdose Requiring Extracorporeal Mechanical Oxygenation
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Introduction: Acute on chronic angle-closure glaucoma with elevated intraocular pressure was well-established etiology of severe eye pain and profound vision loss, if not treated urgently. This case is a recurrent and episodic eye pain with transient visual loss during HD.

Case Description: 64 year-old Caucasian female with comorbidities including poorly controlled insulin dependent type 2 diabetes, uncontrolled hypertension, obesity. She is on intermittent hemodialysis three times weekly the last 5 years. She was previously followed by a retina specialist for proliferative diabetic retinopathy with subsequent neovascular glaucoma. Initial onset approximately 1 year prior, with episodic eye pain, decreased visual acuity, and increased intraocular pressure. The right eye had well-documented hypotony and decreased visual field post dialysis. She had a refractive surgical procedure performed for phacoemulsification with IOL implantation. Her visual acuity improved in the right eye. However, she subsequently developed eye tenderness only during HD. Hemodialysis (HD) may lower plasma osmolality at a faster rate than changes in ocular osmolality can adapt. Here we are presenting two cases of ESRD patients who repeatedly develop eye pain only during HD.

Discussion: The effect of hemodialysis (HD) on intraocular pressure (IOP) is variable and the exact mechanisms are still not clear. Previous reports in the literature suggest both increased and decreased intraocular pressure during fluid shifts associated with hemodialysis. Argon Laser Photocoagulation is known to reduce angle neovascularization induced by peripheral retinal ischemia in Neovascular glaucoma patients, IOP reduction is typically achieved with topical and systemic medications. Shunting and filtering procedures, including glaucoma valve implants and trabeculectomy surgery, may restore outflow and reduce IOP. After appropriate surgical intervention, the patient reported resolution of symptoms and improved tolerance to dialysis sessions.
Case Description: A 33-year-old female weighing 63kg presented after ingestion of approximately 100g of guanua powder (22g of caffeine). She presented with tachycardia (140-170 BPM) and severe hypotension (blood pressure 50/40 mmHg) resistant to 4 vasopressors at maximal dose. She required extracorporeal membrane oxygenation (ECMO). Baseline renal function was normal. IHD was initiated with blood flow rate (BFR) 200ml/min and dialysate flow rate (DFR) 500ml/min, which was gradually increased over 4 hours to a BFR of 400ml/min and DFR of 800ml/min; IHD continued for an additional 4 hours at this rate. During this 8-hour IHD treatment, her initial 4 pressor doses were halved, and she was transitioned to CVVHDF; the caffeine level was pharmacologically unavailable. However, after 12 hours of CVVHDF, the patient did not experience continued hemodynamic improvement, so IHD was reinstituted for 12 hours. Following this second prolonged session of IHD, she was weaned down to moderate doses of just two pressors. She was then transitioned back to CVVHDF for an additional 36 hours, at which time she was able to come off ECMO and all pressors. She had a full neurologic recovery. We later received a serum caffeine level of 425mg/L (drawn soon after arrival at the hospital), which is the second-highest level ever reported; the established lethal concentration is 80ng/mL.

Discussion: Despite continuous dialytic therapies being generally favored in patients with severe hemodynamic instability, a combination of IHD and CVVHDF may be used for hemodynamically unstable patients who ingest extremely high dose of caffeine. However, in such patients, continuous therapies are unlikely to supplant prolonged and repeated IHD treatment sessions.

PO0904
Anaphylaxis Secondary to Citric Acid Allergy in ESKD Patients
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Introduction: Dialysis reactions are common in ESKD patients undergoing hemodialysis (HD). We report first case of anaphylaxis related to citric acid solution used for dialysis disinfection & descaling.

Case Description: 61-year-old male with history of ESKD on HD for 7 years, presented after missing dialysis. Patient underwent urgent HD upon presentation and developed signs of angioedema within first 30 minutes, requiring nasal intubation & treatment with epinephrine, steroids & antihistamine. While intubated and hypotensive, patient had uneventful Slow Low Efficiency Dialysis. Angioedema was presumed secondary to anitiemetics, which patient required due to severe nausea shortly after starting HD. Post extubation, patient developed similar reaction with milder symptoms with HD that responded to stopping HD and medical therapy. He had normal complement and mildly elevated tryptase. He was presumed to have a dialyzer reaction therefore, the dialyzer was changed from Revaclear to REXEED & it was tolerated well. He had similar severe reaction a week later while using the REXEED dialyzer. Investigations showed elevated anti-ethylene oxide antibodies (ETO) but clinical significance was questionable given the reaction only developed in inpatient setting. Later we discovered that dialysis machines are disinfected/descaled differently between inpatient & outpatient dialysis, even though both utilize citric acid, which might have led to more exposure to citric acid solution in inpatient setting. For next 2 weeks, patient was dialyzed using different combinations of dialysis machines, dialyzer & dialysis circuits including ones sterilized with ETO, however, all machines were disinfected/descaled using a combination of bleach & heat. After elimination of citric acid, patient had no further anaphylactic reaction.

Discussion: Dialyzer membrane reactions have been commonly described as Type A reactions mediated by dialyzer membrane (IgG mediated) and Type B membrane reactions mediated by complement activation. In our case clinical significance of ETO antibody was not clear, & angioedema was eliminated after removing citric acid from the machine disinfection process. Industrial citric acid mediated angioedema has not been reported before, & it might be an important mediator of allergy in ESRD, & careful review of the dialysis machine preparation should be reviewed in every case of severe allergic reaction.

PO0905
An Unexpected Cause of Colitis
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Introduction: Gastrointestinal manifestations are common among patients with advanced kidney disease. However, uremia associated colitis is rarely described in patients with ESKD. We present a unique case of uremic pancolitis in a patient with ESKD of unknown cause.

Case Description: An 18-year-old male with a history of asthma was admitted with nausea, vomiting and diffuse abdominal pain. He had no fever, arthralgias, rash, respiratory symptoms, or diarrhea. Mild peripheral edema and flapping tremors were noted on physical examination. Laboratory blood tests revealed severe kidney injury (creatinine 18.2 mg/dL, BUN 129 mg/dL). Urinalysis was positive for blood and protein. Immunologic and infectious serologies were unremarkable. An abdominal CT scan detected two small atrophic kidneys and diffuse severe bowel wall thickening of the colon with thumb printing noted (Figure 1), mimicking a pseudomembranous colitis pattern. Abdominal ultrasound revealed severe edema along with high vascularization of the colon wall. Uremia associated colitis was suspected due to the patient’s extreme uremic state and hemodialysis was initiated. Following three weeks of hemodialysis, an abdominal ultrasound showed a significant improvement in edema and vascularization of the colon wall.

Discussion: Patients with advanced CKD often have a variety of gastrointestinal symptoms. However, severe uremic colitis mimicking pseudomembranous pattern is extremely rare in ESKD. Extensive literature review revealed only single case report of uremic pancolitis in a patient with severe kidney injury related to IgA nephropathy. With the improvement of care of patients with kidney disease, uremic colitis is rarely seen in the routine nephrology practice. However, it should be included in the differential diagnosis and evaluation of patient with ESKD, particularly if other more frequent etiologies of colitis have been excluded.

PO0906
Reverse Shoulder Arthroplasty in Dialysis Amyloidosis
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Introduction: The use of high-flux over cuprophane dialyzers, has led to Beta-2 microglobulin amyloidosis (B2M) becoming rare in long term hemodialysis (HD) patients. Amyloid fibers embed systemically, skeletal involvement producing bone cysts, tendinopathy and fractures.

Case Description: A 65-yr male on chronic HD for 30 years presented with progressive, right (R) shoulder intractable pain and limited range of movement (ROM). X-ray/MRI identified severe glenohumeral osteoarthritis (OA), tendinopathy and large irreparable rotator cuff tear. Past history included heart failure, pulmonary hypertension, hepatitis C, severe secondary hyperparathyroidism and chronic anemia. Surgical history included bilateral (b/l) total hip arthroplasties, b/l carpal tunnel release, R nephrectomy for renal cell carcinoma in renal cystic disease. Due to the intractable pain, disability and failure of physical therapy and corticosteroid injection therapy he underwent reverse shoulder arthroplasty. Operative findings showed large soft tissue deposits about the subscapularis, glenoid and labrum, attributed to amyloid. Histology of intra-articular soft tissue, labrum and synovium confirmed amyloid (apple-green birefringence by Congo Red Staining) with focal calcium pyrophosphate deposition. Undecalcified histology of humeral head showed moderate secondary hyper-parathyroid bone disease with peri-articular amyloid deposits. Following surgery patient noted marked improvement in pain and partial improvement in shoulder ROM.

Discussion: No treatment exists for HD patients with B2M, ineligible for kidney transplant. Physicians are tasked with treating clinical manifestations that severely impact quality of life (QOL). Concern for adverse outcomes and paucity of surgical precedent should not deter appropriate surgical intervention. This patient illustrates the clinical and surgical decision-making targeted to improving (QOL).
PO0907

Prediction of Severe Gastrointestinal Bleeding Events in Hemodialysis: Collaborative Development of Machine Learning Model Within INSPIRE

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Background: INSPIRE is an initiative on advancing patients’ outcomes in renal disease (INSPIRE) is an academia and industry collaboration set forth to identify critical investigations/models needed to advance the practice of nephrology. As an inaugural effort, INSPIRE group aims to develop a machine learning (ML) model that can identify a hemodialysis (HD) patient’s 30-day risk for hospitalization due to gastrointestinal (GI) bleeding.

Methods: We used data from adult (age ≥18 years) HD patients (Jan 2017-Dec 2020) in the United States to build a XGBoost model considering 2,292 variables for classification of 30-day GI bleed hospitalization risk. Data were randomly split in 50%:20%:30% ratio for model training, validation, and testing. Unseen data by model classification of 30-day GI bleed hospitalization risk. Data were randomly split in 50%:20%:30% ratio for model training, validation, and testing. Unseen data by model (testing) was used for assessing performance via area under the curve (AUC) and feature importance of predictors via Shapley (SHAP) values.

Results: Among 58,187 HD patients included in the testing dataset, 1,150 had a GI bleed hospitalization event. The model showed AUC=0.67 and top predictors of a GI bleed hospitalization in 30 days were the minimum hemoglobin level in prior 180 days, time since prior GI bleed hospitalization, and higher vitamin D levels (Figure 1).

Conclusions: ML model appears to have suitable performance for identifying a patient’s 30-day risk for GI bleed hospitalization. Albeit further model iterations/tuning are needed, ML techniques that account for collinearity and missingness hold promise for early detection of potentially avoidable GI bleeding admissions. Model identified an important association between higher vitamin D levels and GI bleeding events, which is consistent with the increasing evidence suggesting antithrombotic and anticoagulant actions of vitamin D derivatives.

Funding: Commercial Support - Fresenius Medical Care

PO0908

Artificial Intelligence-Driven System to Automatically Identify Arterial Oxygen Saturation Saw-Tooth Pattern in Hemodialysis

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Background: Sleep apnea (SA) is a condition where normal respiration is disrupted by episodes of apnea because of disturbed respiratory control (central SA) or upper airway obstruction (obstructive SA). Arterial oxygen saturation (SaO2) saw-tooth pattern indicate respiratory instability. We aimed to automatically identify patients with repetitive episodes of intermittent SaO2 saw-tooth pattern.

Methods: The analysis was based on SaO2 recordings taken at a frequency of 0.1 by the Crit-Line® device (Fresenius Medical Care, Waltham, MA). Segments of 30 consecutive SaO2 recordings (i.e., 5 minutes of SaO2 time series) were adjudicated and categorized as (a) no saw-tooth pattern; (b) mild saw-tooth pattern; and (c) severe saw-tooth pattern (examples shown in Figure 1). We used one-dimensional convolutional neural networks (1D-CNN) for time series classification. We randomly assigned SaO2 time series segments to training (80%) and validation (20%) sets, respectively.

Results: We analyzed 89 hemodialysis (HD) treatments with 4,075 adjudicated SaO2 time series segments. Their distribution across the 3 categories was 78% (a), 11% (b), and 11% (c), respectively. In the validation data set of 815 SaO2 time series segments, we achieved an accuracy of 93.9%, 95.8% of category (a), 91.2% of category (b) and 82.8% of category (c) pattern were classified correctly by our 1D-CNN.

Conclusions: Our 1D-CNN algorithm accurately classifies saw-tooth pattern in SaO2 time series recorded in HD patients. The SaO2 pattern classification could be performed in real time during an ongoing HD treatment and provide timely alert in the event of respiratory instability.

Funding: Commercial Support - Fresenius Medical Care North America

Panel A: Intradialytic SaO2 saw-tooth pattern. Panel B to D: SaO2 time series with no saw-tooth pattern (B); mild saw-tooth pattern (C); severe saw-tooth pattern (D)

PO0909

Leveraging Dynamic Data to Predict Mortality Risk in Patients Undergoing Chronic Hemodialysis

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Background: Predictive models of mortality on HD typically use data collected at HD initiation. This is a missed opportunity that does not leverage the regularly collected data at HD treatments and is not reflective of how models would be used in practice. We compare performance of a risk model that uses static baseline data at incidence vs data at HD treatments and is not reflective of how models would be used in practice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0910
Machine Learning Classification of Tweets for Patient Dialysis Experience
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Background: Popular microblog (e.g. Twitter, Facebook) services provide a continuous stream of public health information. This data has been used to monitor viral spread, medication adherence, and false health information. There are thousands of posts on Twitter daily regarding personal dialysis experience, access, and side effects. While these posts include valuable public health information, evaluating these posts to meaningfully assist dialysis patients is difficult as there are even more tweets mentioning dialysis in a professional context. We aimed to modify a state of the art natural language model to classify posts about dialysis as personal or professional.

Methods: We filtered posts containing the word dialysis. Posts were manually labeled as personal or professional by a nephrologist depending on the context dialysis was mentioned. The data was randomized and split for 60% training, 20% validation, and 20% testing. The text was preprocessed to remove extraneous characters and input into a Bidirectional Encoder Representations from Transformers (BERT) model for fine tuning, and a term frequency inverse document frequency vectorized Multinomial Naive Bayes Classifier.

Results: We collected 6011 tweets from May 3, 2021 to May 14, 2021. 1000 tweets were randomized and labeled. 57% were categorized as personal. BERT and Naive Bayes models attained 88% and 82% accuracy, respectively, on the testing data. The BERT model classified far less false negatives with a small increase in false positives (Figure 1).

Conclusions: BERT’s semantically rich word embeddings can enhance social media mining algorithms on dialysis content. We show superiority of a BERT model over a traditional count-based language model. This method can be easily applied as a pre-processing step to remove noisy posts to better study dialysis and other health trends in social media. This novel processing task and pipeline have broad clinical and public health implications for reducing the amount of data and time required for accurate, real-time monitoring of patient level posts.

PO0911
Automating Dialysis Machine Alarms During Sustained Low-Efficiency Dialysis (SLED)
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Background: Sustained low-efficiency dialysis (SLED) with regional citrate anticoagulation (RCA) is frequently employed at our institution. RCA requires constant monitoring because a dialysis machines alarm that stops the blood pump (BP) or bypasses dialysate leads to an increased rate of citrate infusion into the patient, with consequence of ionized hypocalcemia. To enhance safety and surveillance efficiency, we developed an innovative computer/phone system that identifies SLED machine alarms and notifies clinical care staff directly via proprietary phone network.

Methods: In 2017, we linked onboard SLED computer Wi-Fi systems to the hospital’s internal phone network (ASCOM). An alarm recorded by the SLED machine’s computer delivers an email to a dedicated email account that is subsequently transmitted to the ASCOM MailGate System. Mailgate produced and relayed text message alerts to dedicated ASCOM phones of dialysis technicians or nurses. Importantly, no additional training or changes in workflow are required for adoption of this method.

Results: This innovation has increased safety and efficiency. Response times for machine alarms improved and downtimes on dialysis were reduced, increasing dialysis dose of dialysis. To ascertain end-user satisfaction of the automated alarming system, we conducted a survey that demonstrates high-level satisfaction with the system (Table 1.)

Conclusions: Currently, no medical alert companies connect dialysis machine information to a medical alert phone system. ASCOM provides wireless messaging systems for dedicated hospital applications. Notably, ASCOM does not directly connect to dialysis machines. In addition, Email Alerts can be browsed by managers for archival retrieval, quality and safety report generation, and investigation of unanticipated events.

Funding: Clinical Revenue Support

PO0912
Users of a Web-Based Communications Platform for Care Coordination of Hospitalized Dialysis Patients
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Background: Better care coordination between dialysis clinics and hospitals may improve outcomes among hospitalized dialysis patients. To fill the gap created by separate electronic health record systems across the two settings, we rolled out a web-based communications platform (“DialysisConnect”) in four dialysis clinics and one hospital in Atlanta. Here, we examine usage patterns of DialysisConnect.

Methods: DialysisConnect included automatically uploaded clinical information from dialysis clinics, forms for entering critical admission and discharge information, and a direct communications channel. Two nephrologists and two hospitalists served as project champions at the dialysis clinics and hospital, respectively. DialysisConnect was made available to 106 potential users (hospitalists, nephrologists, advanced practice providers (APPs) at the hospital and dialysis clinics, care coordinators (hospital), and nurses/nurse managers (dialysis clinic)) starting 10/29/20. Descriptive statistics were used to describe patterns overall and by user role through 4/15/21.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0913

Family-Friendly, Work-Friendly, Home-Hemodialysis and In-Center Hemodialysis Hybrid: The First of Its Kind

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Introduction: Hybrid dialysis is traditionally defined as the combination of peritoneal and hemodialysis (HD) in patients with end-stage renal disease. Its reported use is quite limited outside of Japan. We recently encountered major family-related and employment-related constraints that prevented a 39-yo man with ESRD on home HD from completing the four-times weekly HD treatments with HD inadequacy and worsening of patient’s physiology. We successfully switched him to a new hybrid of twice-weekly HD + twice weekly In-Center HD. This is the first such report.

Case Description: A 41-yo male with ESRD secondary to SLE and hypertension on home HD, 4 x weekly, for some years experienced family-related constraints including non-availability of day-care for two young children due to COVID-19 pandemic, spousal illness and non-family-related challenges with morning travel and was missing his HD sessions. The result was inadequate HD delivery and worsening laboratory indices. He now receives 2 in-center HD treatments on Tuesdays and Thursdays, and 2 home HD treatments, once during the weekend and once during the week. This was started in February 2021. Each HD session lasts for 3.5 hours, 2000 units Heparin bolus, and his left brachiocephalic AVF is accessed by the button-hole method. The Home Dialysis Staff coordinates his dialysis care. Standardized Kt/V for May 2021 was 2.6.

Discussion: Hybrid dialysis is traditionally defined as the combination of peritoneal and HD in patients with ESRD. A 2020 Italian report described another type of hybrid dialysis that consisted of once-weekly in-hospital HD and home peritoneal dialysis to limit patient exposure to the hospital environment during the COVID-19 pandemic. We have described the successful application of a new Hybrid HD system that combined Home HD + In-center HD. To our knowledge, our report is the first of its kind and was designed and implemented primarily for the purpose of overcoming increasing family and employment demands on the patient. This new hybrid dialysis option was designed to facilitate a family-friendly work-friendly HD on a long-term continuous basis. The patient’s family members, two young children and his employers are happy and very satisfied. Simultaneously, the patient has continued to do well with adequate dialysis and meeting all the required goals of management in the past 3 months.

PO0914

Triple I Study: Hubs of Care Survey

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Background: The Can-SOLVE CKD Triple I Study identified continuity of care; access to a primary care provider (PCP) in the hemodialysis (HD) unit; and access to care for other medical conditions as key challenges to in-centre HD care (www.betterkidneycare.ca). The Hubs of Care project aims to address these challenges by incorporating health care providers (HCPs) from other settings in the HD unit; firstly, we identify current practice, potential interest and need and desire for different HCPs in HD.

Methods: A cross-sectional self-reported survey administered Feb-May 2021 with HD patients and staff at four academic sites across Canada. Eligible participants included adults fluent in English or French who could complete the survey independently. The survey asked which HCPs are currently in HD units, which additional HCPs would like to see a PCP in the HD unit; of those, 87% prefer in-person and 13% prefer virtual. Qualitative analysis reveals privacy concerns due to the open concept of HD Units; however, the concept of bringing HCPs into the HD unit is regarded as beneficial and time-saving.

Conclusions: In this cross-sectional survey both HD patients and staff identified that, despite privacy concerns, bringing HCPs that provide foot, diabetic and mental health care into the HD unit was a priority with potential for benefit.

Funding: Government Support - Non-U.S.
PO0016
Impact of Medication Reconciliation by a Dialysis Pharmacist
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Background: Medication reconciliation (MR) improves patient outcomes, reduces cost, and is a reporting measure for the CMS End-Stage Renal Disease Quality Incentive Program. Most dialysis facilities do not have a clinical pharmacist to perform MR. The purpose of this study is to evaluate the impact of a pharmacist performing MR and medication management for patients receiving outpatient chronic hemodialysis at an academic institution.

Methods: We conducted a retrospective study from 10/1/18 to 11/2/20 to determine if MR by a pharmacist reduced medication discrepancies (MDs) and medication related problems (MRPs) over time. Secondary outcomes were to describe the type of MDs, type and severity of MR, impact of a pharmacy delivery service, and number of emergency department (ED) visits and hospitalizations pre- and post-pharmacist integration.

Discrepancies were categorized as: unintentional discrepancy, unintentional intentional discrepancy, and MRPs. MRPs severity was categorized using the National Coordinating Council for Medication Error Reporting and Prevention index. Descriptive statistics were calculated for each variable and a repeated measures ANOVA test was conducted to determine if MDs or MRPs changed over time.

Results: A total of 135 patients with 479 unique pharmacist encounters were included. The mean (SD) age was 61.7 (14) years, 58% were male, 65% caucasian, mean (SD) time on dialysis was 12.6 (6.4) years and most common comorbidities were diabetes and hypertension. The pharmacist conducted 3.5 MR/ patient with a mean time spent of 39.7 (16) minutes and 16% required an interpreter. Unintentional discrepancies were noted in 53% encounters, undocumented intentional discrepancies in 71%, MRPs in 59% but decreased significantly from the first to the second encounter (1.9 vs 0.9, 1.9 vs 1.2, and 1.1 vs 0.5 per patient, respectively, p<0.05). Most common MRPs types included non-adherence, prescription renewals, and excessive drug doses. Over half (54%) were enrolled in a pharmacy delivery service and had significantly fewer undocumented intentional discrepancies compared to non-enrollees (p<0.05). ED visits and admissions pre- and post-pharmacist integration were not statistically different.

Conclusions: Integrating a pharmacist into a hemodialysis unit enabled effective medication reconciliation and management to significantly reduce medication discrepancies and problems, and improve safety.

PO0098
Feasibility Study of Wrist-Based Wearable Activity Tracker in Hemodialysis Patients
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Background: Increased physical activity (PA) is associated with reduced risk of cardiovascular disease which is prevalent in hemodialysis (HD) patients. Wearable activity trackers (WAT) allow remote monitoring of PA. We aim to explore the feasibility of using a WAT for 1 year in HD patients.

Methods: HD patients from 4 NYC clinics were enrolled on a rolling basis starting June 2018 and followed for up to 1 year. Ambulatory patients ≥18 years, on maintenance HD, and owning a mobile device were included. Each patient was provided with and taught how to use the Fitbit Charge 2. A stepwise intervention plan was used to assess feasibility (Figure 1). We used Kaplan-Meier analysis to determine mean and median time to withdrawal for non-compliance (TW) and predictors of TW were assessed by univariate Cox Regression.

Results: 119 patients were enrolled into the study. Patients were 54±12 years old, 59% African American, 37% lived alone, and 54% had an education level of college and above. 16% of patients were withdrawn for non-compliance. Mean and standard deviation TW was 175 ± 103 days. Median and interquartile range of TW was 133 and 181 days (98 to 280 days), respectively. The probability of not being withdrawn for non-compliance is shown in Figure 2. Age, gender, race, living status, and education were not associated with non-compliance.

Conclusions: A small portion of patients were continuously non-compliant with wearing/syncing their Fitbit devices in our study. Based on a low risk (<20%) of being withdrawn for non-compliance, we determined that it is feasible to use a wrist-based wearable device in HD patients for up to a year. However, prolonged use of these devices may require additional counseling to patients.

Funding: Commercial Support - Fresenius Medical Care

PO0917
Interim Analysis of the Extension of Tablo Treatment Duration (XTEND) Study
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Background: The Tablo® Hemodialysis System (Tablo) is an all in one, easy-to-learn device featuring integrated water purification, on demand dialysate production and two-way wireless data transmission and is approved for use in the acute, chronic and home settings. Prior reports have demonstrated Tablo’s ability to achieve clinical goals, seamlessly integrate into hospitals and reduce cost across a wide range of treatment times. Extension of the Tablo cartridge to 24 hours (extended therapy; “XT”) allows even greater flexibility for prescribers in the acute setting. The objective is to report on the experience with Tablo extended therapy between 12 and 24 hours utilizing an interim review of the XTEND study (NCT04912050).

Methods: Nursing staff were trained during a single training session on Tablo XT. After a run-in period of 5 treatments, Tablo data were collected via real-time transmission to a cloud-based, HIPAA compliant platform and reviewed by site staff. Clinical treatment success was defined as either ending within 10% of prescribed time or site investigator assessment that all patient treatment goals were met.

Results: Fifty (50) Tablo XT treatments had a median prescribed treatment time of 24 hours and a median achieved treatment time of 23.5 hours. Median cartridge use was 1.0 per treatment. Clinical treatment success was 84%. Treatments ended due to clotting/ clogging were 4% (2 of 50). Median total ultrafiltration (UF) rate was 1.7 mL/kg/hr. Clinically significant alarms occurred at a median rate of 7 per treatment with a resolution time of 14 seconds. Most frequent alarms experienced were arterial and venous pressure (39% and 58%, respectively), of which none resulted in an end treatment.

Conclusions: Tablo’s XT successfully achieves prescribed treatment time and favorable ultrafiltration rates with minimal therapy interruptions from alarms or cartridge changes. This data demonstrates the effectiveness of Tablo’s newly expanded versatility in achieving personalization of treatments necessary for unstable patients and enabling successful delivery of extended therapy with minimal clotting. Tablo’s 24-hour therapy meets the needs of critically ill patients that require renal replacement therapy for greater than 12 hours.

Funding: Commercial Support - Outset Medical, Inc.
Glycemic Status Ascertained by Continuous Glucose Monitoring in a Prospective Hemodialysis Cohort


Background: Hemodialysis (HD) patients with diabetes are at heightened risk of hypo- and hyperglycemia due to multiple pathways. While self-monitored blood glucose is the standard approach for glucose assessment in HD patients, it may not adequately capture glycemic status given its infrequent nature. We thus sought to measure glucose levels using continuous glucose monitoring (CGM) as a more frequent (every 5-minutes), convenient, and automated method of glycemic status in a prospective HD cohort with diabetes.

Methods: Among 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneous protocolized glucose measurements using 1) CGM measured by Dexcom G6 devices vs. 2) blood glucose levels using capillary fingertip or venous blood glucose, with the latter measured 4± times per day (before each meal and at night), plus every 30 minutes during HD (total of 6-8 measures during HD). Using American Diabetes Association (ADA)-defined CGM targets, we examined the prevalence of patients achieving the recommended percentage (%) of CGM levels in the ranges of <54, ≥70, 70-180, ≥180, and ≥250mg/dL (ADA target % of glucose levels <1%, <4%, >70%, <25%, and >5%, respectively).

Results: Whereas 64% of CGM measurements (N=9444) were within target glucose range (time in range [TIR] 70-180mg/dL), 80% of blood glucose levels (N=100) were within TIR. The proportion of patients achieving the recommended % of CGM measurements within ADA-defined glycemic ranges of ≥250, >180, 70-180 (target range), <70, and <54mg/dL were 67%, 44%, 44%, 89%, and 78, respectively.

Conclusions: In a cohort of hospitalized diabetic HD patients who underwent concomitant CGM and blood glucose measurements using the Dexcom G6 remote access system, blood glucose testing overestimated the % of time patients were in target glycemic range as compared with CGM. CGM showed that less than half of patients achieved the recommended % of CGM measurements within target range. Further studies are needed to determine whether CGM can improve the glycemic management of HD patients compared to conventional approaches.

Funding: Commercial Support - Dexcom, Inc.

Validation of Automated Sodium Control in a Novel Dialysis System


Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test an automated feedback program designed to regulate the infusion of an alkali needed to maintain proper sodium concentration in a dialysate solution

Methods: A 125L volume of simulated dialysate was circulated at ~400 mL/min and ~37 C through a sorbent cartridge which removed the urea from the solution. The fluid exiting the cartridge had no Ca, Mg or K. These chemicals were reinfused through a pump in a solution containing Ca, K and Mg salts. A conductivity sensor (cond) was used in a feedback control of the alkali infusion pump. The feedback control adjusted the pump flow rate to maintain the conductivity of the infusate at 14.1 mS/cm. The sensor was programmed from a curve model of the alkali over time from previous experiments. Occasional spikes of Na+ were programmed from a curve model of the alkali over time from previous experiments.

Results: The results are depicted in table 1. TP1, the mean sodium concentration [Na+] in the dialysate at pump 1, after mixing in a 125L tank was in the range 139.8 – 141.7 mEq/L. TP2, the mean dialysate [Na+] at pump 2 after leaving the sorbent filter was 124.2 (+/-2.4) mEq/L. This correlates with cond1 and was 12.8 (+/-0.4) mS/cm. TP3, the mean dialysate [Na+] after being replenished with the alkali solution immediately prior entering the tank for remixing was 139.5 (+/- 1.9) mEq/L and correlated with cond2 of 14.1 mS/cm.

Conclusions: The results validate the accuracy of the conductivity sensor in correctly regulating the alkali infusion.

Funding: Commercial Support - Diality Inc.

Diffusion of Therapeutic Effects Between Roxadustat and Daprodustat, HIF-PH inhibitors, Depending on the Blood Type in Hemodialysis (HD) Patients

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Background: Human blood group antigens are glycoproteins and glycolipids expressed on the surface of red blood cells and a variety of human tissues. This study aimed to determine if there is an association between ABO blood type and the efficacy of HIF-PH inhibitors. Roxadustat and daprodustat are potent inhibitors of HIF-PH and capable of stimulating erythropoiesis in patients with impaired renal function. These two compounds are reported to act mechanistically similar but display differences in their effects on cells, and the differences may affect their efficacy in the treatment of renal anemia in HD patients. In this study we compared the response rate by blood type of roxadustat and daprodustat, respectively.

Methods: Sixty-eight HD patients treated with roxadustat (20-100mg, 3/week) and ninety-five treated with daprodustat (1-12mg, daily) were recruited in our observational study. We defined >1.5g/dL increase in hemoglobin as effective, and <1.5g/dL decrease as ineffective.

Results: As shown in the figure, type A had the highest response rate at 47% in HD patients treated with roxadustat. On the other hand, type O had the highest response rate at 55% in those who were treated with daprodustat.

Conclusions: We found the association in the effectiveness of roxadustat on the treatment for anemia in HD patients in type A, while the effectiveness was higher in type O treated with daprodustat. The results suggest that the therapeutic effect of HIF-PH inhibitors may differ depending on the blood type.

Funding: Private Foundation Support
PO0922

Nanostructured Capillary Membranes for Size-Selective Hemofiltration
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Background: Size-selective separations offer potentially transformative advances for hemofiltration. In the context of hemodialysis, the tradeoff between selectivity and permeability often results in large package sizes and high driving pressures that limit wearable and implantable options of therapy. Here, we report on composite membranes with vertically aligned precise nanoscale capillaries with improved permeability.

Methods: Arrays of carbon nanotubes (CNTs) were synthesized via chemical vapor deposition and the catalyst composition was carefully selected to achieve a uniform distribution of diameters. The area between the CNTs was filled with a polymer to form a membrane. The CNT membranes were backed with microporous silicon supports and mounted into a filtration cell. Hydraulic permeability was calculated from gravimetric flow rates at stepped transmembrane pressures. Size-selectivity was measured by filtering fluorescently-labeled polydisperse Ficoll in phosphate-buffered saline. Size-specific Ficoll concentrations in feed and filtrate were measured by size-exclusion chromatography.

Results: CNT membranes membrane exhibited a cut-off of 6nm and the measured hydraulic permeability was 102.3 ml h⁻¹ m⁻² mmHg⁻¹ compared to published data of 30 ml h⁻¹ m⁻² mmHg⁻¹ for conventional high flux dialyzers. CNT membranes retained large molecules while passing small and medium-sized molecules. Sieving coefficient at 2 nm, approximately the size of β2 microglobulin, was unity (Figure).

Conclusions: The CNT membranes provide excellent middle molecule clearance and hydraulic permeability multiples of conventional membranes. Further research is necessary to move to clinically implement this technology.

PO0923

Delivered Dialysate Potassium Is Higher Than What Is Prescribed When High Sodium and Low Bicarbonate Are Prescribed
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Background: Most hemodialysis machines utilize the 3-stream method of making dialysate. In hospital settings, dialysate prescriptions are customized to the clinical setting. We determined the differences between delivered and prescribed dialysate K⁺ in unusual prescriptions.

Methods: Dialysate samples drawn 15 minutes into HD were analyzed via indirect ion-specific electrodes for Na⁺, K⁺, and HCO₃⁻. 5200 HDs with extremes of ordered Na⁺ and HCO₃⁻ were analyzed. Outcome was measured versus ordered K⁺. Analysis used ANOVA using SPSS.

Results: Means of the difference between measured and ordered K⁺ and Na⁺ are shown in figure 1. For K⁺ there was significant difference amongst the groups (p<0.001). There were no differences amongst the groups for Na⁺.

Conclusions: When a very high Na⁺ is prescribed along with a low HCO₃⁻ the dialysate K⁺ remains close to prescribed Na⁺. As the acid concentrate contains both Na⁺ and K⁺, a high Na⁺ and low HCO₃⁻ prescription will use a relatively more of the acid concentrate and less of the bicarbonate concentrate. Dialysate prescriptions with a high Na⁺ and low HCO₃⁻ increased delivered dialysate K⁺ by an average of 0.5 mEq/L; we observed some HDs where dialysate K⁺ was 1 mEq/L higher than prescribed.

Figure 1: Means of the difference between measured and ordered K⁺ and Na⁺.

PO0924

Urea Clearance Performance in a Modified Batch Dialysis System

Background: Urea clearance is the key measure of dialysis adequacy. The Diality Hemodialysis Machine will provide good clearance performance to ensure an adequate dose of dialysis. Specific Aims: To assess clearance performance during simulated dialysis utilizing a novel modified batch process. In this setup, dialysis was conducted by alternating dialysate delivery from subsequent two-liter reservoirs.

Methods: Simulated dialysis sessions were conducted utilizing blood flowsrates of 300 ml/min, dialysate flowsrates of 500 ml/min and no ultrafiltration. Dialysis occurs off of a two-liter batch of dialysate. Once two liters of dialysate has been circulated through the dialyzer, the spent dialysate is discarded and dialysis switches to a separate two-liter reservoir of dialysate while the first reservoir is drained and filled with fresh dialysate. A single compartment simulated patient was created by combining 50 L of DI water with a 20mM concentration of urea. Simulated blood samples were collected at the dialyzer inlet and outlet and dialysate samples collected at the dialyzer outlet to determine urea concentrations over the course of the simulated treatment.

Results: The results are provided in Figure 1. The urea concentrations in the blood decreased over the course of treatment as expected given the stated clearance values of the dialyzer used in the simulated treatment.

Conclusions: The initial experiments using a modified batch system show promising urea clearance. Future tests will better characterize performance compared with conventional devices that do not use a modified batch configuration.

Funding: Commercial Support - Diality Inc
PO0926

Comparative Effectiveness Between Novel Medium Cut-Off Membrane Hemodialysis and Mixed-Dilution Online Hemodiafiltration on Middle Molecule Uremic Toxins Reduction: A Prospective Cross-Over Study
Jirarat Eiamcharoenying, Pajaree Charityavilaskul, Kullaya Takivakatkarn, Paweesa Susantitaphong, Yingyos Avihingsanuk, Somchad Eiam-On, Khajohn Tiranathanagul. King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Background: Mixed-dilution online hemodiafiltration(mixed HDF), one of the best hemodialysis(HD) modes, provides superior removal of middle molecule uremic toxins to standard HD using high flux dialyzer. Due to the limited availabilities and high cost of HDF, we performed standard HD utilizing a novel medium cut-off membrane with a larger pore size and compared the effectiveness in removal of middle molecule uremic toxins with mixed HDF.

Methods: A prospective cross-over randomized controlled trial was conducted in 14 prevalent HDF patients who were randomly allocated into group1 (n=7): mixed-dilution online HDF with high flux dialyzer ELISIO21H and group2 (n=7): standard HD with MCO membrane, Theranova 500. In this 8-week study, the primary outcome was a reduction ratio( RR) of Beta2-microglobulin (B,M). Other small to middle molecules and protein-bound uremic toxins reduction ratio, dialysate albumin loss, and nutritional parameters were also compared.

Results: In this 8-week study, B,M RR from both modalities was higher than the survival benefit cut-point of 80%. In comparison, B,M RR was slightly lower but significant in MCO HD than mixed HDF (82.57±5.34% vs 85.12±3.87%, respectively) with the mean difference of 2.59 (95% confidence interval [CI], -0.07 to -1.03; P<0.001).

The spKt/Vurea and URR, a small uremic toxin removal marker, were comparable. kFLC and Indoxyl sulfate RR also were similar in mixed HDF and MCO HD. Whereas RR of the larger middle molecule uremic toxin, Alpha_M and JFLC was lower with mixed HDF compared to MCO HD (30.13±15.90 vs 41.49±11.46 and 40.85±13.92 vs 50.81±13.18, respectively; P<0.001).

Conclusion: Mixed HDF and MCO HD provided the RR values of B,M and small uremic toxins above the respective cutpoint. Despite mixed HDF provided higher B,M RR, MCO HD also provided more performance in the clearance of the larger middle molecules, particularly Alpha_M and JFLC. However, mixed HDF loss lower albumin than MCO HD. Therefore, both techniques can be used as alternative options.

Funding: Government Support - Non-U.S.

PO0927

Clearance of Protein-Bound Uremic Toxins on the Tablo Hemodialysis System
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Background: The Tablo Hemodialysis system (Tablo) is an all in one, easy-to-learn device. While clearance of small and middle molecules has been documented in modern dialysis, the clearance of Protein Bound Uremic Toxins (PBUTs) merits further exploration. Clearance of albumin bound toxins such as indoxyl sulfate (IS) and p-cresol sulfate (PCS) can be limited in dialysis where removal is based on molecular size. Although a clear association has yet to be demonstrated, PBUTs have been considered to be a possible cause of adverse outcomes in patients requiring renal replacement therapy.

Methods: A simulated hemodialysis treatment using Tablo was performed with solution of bovine serum albumin and urea. PCS and IS were added to the solution to maintain a constant concentration. A screening design of experiment was performed utilizing the factors of dialysis flow rate (Qd), blood flow rate (Qb), and ultrafiltration rate (UF). After each factor was changed and allowed to equilibrate, samples were collected from the venous, arterial and spent dialysate lines. Samples of Urea, PCS and IS were utilized for determining cut-point. Despite mixed HDF provided higher clearance, albumin levels were not different.

Conclusions: Mixed HDF and MCO HD provided the RR values of B,M and small uremic toxins above the respective cut-point. Despite mixed HDF provided higher B,M RR, MCO HD also provided more performance in the clearance of the larger middle molecules, particularly Alpha_M and JFLC. However, mixed HDF loss lower albumin than MCO HD. Therefore, both techniques can be used as alternative options.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0928

Dialysis Disequilibrium Syndrome (DDS) in Hemodialysis Patients: Systematic Review
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Background: Dialysis disequilibrium syndrome (DDS) affects patients who have missed multiple dialysis treatments, especially new initiates of hemodialysis (HD), and presents as a rare neurological complication. The conceptual pathogenesis of DDS is likely a result of multiple physiological abnormalities which we explore in this systematic review alongside preventive measures with focus on effective management strategies.

Methods: A literature search was conducted on PubMed/Medline and Embase and included studies if the patient developed DDS irrespective of age and gender. Two independent reviewers conducted the process of article selection with a third reviewer present to resolve any conflicts. The data was analyzed and a summary table was extracted with the following variables: study type, population group, age, patient characteristics, blood and dialysate flow rate, and study outcome. A descriptive analysis was performed analyzing the population size and frequency of symptoms and treatments utilizing the R software.

Results: A total of 49 studies (321 samples) were identified and analyzed. There were 72.4% of patients (based on 48 studies) who reported having DDS with most common symptoms of headache (39.4%), nausea (40.4%), vomiting (39.1%), confusion (66.7%) and seizure (78.6%). Within this sample, 12 studies switched from HD to alternative dialysis modalities including continuous venovenous hemofiltration/haemodiafiltration (CVVH/UVHDF) or peritoneal dialysis (PD) with no further reported DDS symptoms.

Conclusions: We have provided a comprehensive clinical practice points for both the pediatric and adolescent and young adult population; interestingly, DDS was reported more often in the early dialysis era prior to recent advances and improvement of resource allocation. Existing literature shows it is crucial to recognize symptoms of DDS and implement timely prevention to improve outcomes.

PO0929

Protein Loss with Medium Cut-Off and High Flux Dialyzer: A Proteomic Analysis
Xiaoling Wang,1 Xia Tao,1 Leticia M. Tapia Silva,1 Amrish U. Patel,1 Mohamad I. Hakim,1 Nadja Grobe,1 Stephan Thijssen,1 Peter Kotanko,1,2 Renal Research Institute, New York, NY; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Hemodialysis (HD) patients frequently suffer from low serum albumin levels, making dialytic albumin and protein loss a concern. Medium cut-off (MCO) dialysis membranes reportedly show a greater albumin loss compared to high-flux (HiFlux) membranes. To better understand the spectrum of proteins cleared with MCO membranes, we set up an ex vivo dialysis system and perform proteomic analysis of the dialysis membranes.

Methods: Eight liters of human plasma (EDTA added) are split into two 4-liter batches and dialyzed for 4 hrs in single-pass, either with an MCO (Theranova 400) or HiFlux dialyzer (Optiflux F180NR) using a Fresenius 2008T machine. Blood flow was 400 ml/min. Dialysate flow was 600 ml/min for the first 3 hrs and zero for the 4th hr. Ultrafiltration rate was zero for the first 2 hrs and switched to 1 L/hr thereafter. This design allowed us to study three HD modes: diffusion only (2 hrs); diffusion with convection only (1 hr); convection only (1 hr). Dialysates were sampled at multiple time points (Fig 1B).

Results: Three µg of initial plasma and 23 µl dialysate were loaded on an SDS-page gel and silver stained (Fig 1A). Lanes 3 and 4 were from MCO, lanes 4 and 6 from HiFlux. Lanes 3 and 4 were collected 15 mins into dialysis, lanes 5 and 6 at 240 mins. Results show that dialysates contain less high molecular weight proteins compared to plasma, and MCO dialysates contain much more proteins compared to HiFlux dialysates. The strong band at ~62 kD is most likely albumin. Using mass spectroscopy, we can identify 56 different protein species in MCO dialysate. Dialysate protein levels (measured by Bradford assay) with the 3 dialytic modalities are shown in Fig 1B, the total protein losses are listed in Fig 1C. The ratio of protein loss between MCO and HiFlux dialyzers is 17-fold in the convection only mode.

Conclusions: Our results show a higher diffuse and convective protein loss with MCO compared to HiFlux membranes. Further characterization and quantitation of proteins cleared in vivo during HD are necessary to better understand the clinical impact of our ex vivo observations.

Funding: Commercial Support - Renal Research Institute

Figure 1: dialysate protein analysis.

PO0930

Intradialytic and Interdialytic Urea Dynamics in Blood and Cerebrospinal Fluid in Hemodialysis Patients
Xia Tao,1 Lin-Chun Wang,1 Xin Wang,1 Ohnmar Thwin,1 Nadja Grobe,1 Amrish U. Patel,1 Stephan Thijssen,1 Joshua E. Chat,1 Ludovic Debure,3 Thomas Wasienski,2 Peter Kotanko,1,2 Renal Research Institute, New York, NY; ‘NYU School of Medicine, New York, NY; ‘Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Modern, highly efficient hemodialysis (HD) results in rapid decline of blood urea. Urea gradients across the blood-brain barrier (BBB) can drive water movements. A positive urea gradient, i.e. brain urea to plasma urea, can result in brain swelling and impair brain function. We explored the dialytic changes of urea in blood and cerebrospinal fluid (CSF) to better understand intradialytic osmotic gradients across the BBB and provide insights that support the development of brain-protective HD.

Methods: Two HD patients (39 and 26 years old) with ventriculo-peritoneal (VP) shunts were enrolled into this one-week IRB-approved study with a Monday/Wednesday/Friday dialysis schedule. CSF was collected via VP shunt tap 2 hrs before and 2 hrs after HD (Wednesday and Friday), and Tuesday and Thursday. Plasma samples were collected concurrently with CSF and during HD. In addition, the patients underwent test of executive function (Trail Making Test Part B; TMT B) and global cognitive function (Montreal Cognitive Assessment; MoCA) on Monday.

Results: Urea was removed efficiently from patients’ blood by HD. While patient A showed a small post-HD plasma-to-CSF urea gradient, it was highly positive (~ 60 mg/dL) in patient B (Fig 1). TMT B and MoCA score were normal for patient A but not patient B (TMT B 415 sec; TMT B error count: 2; MoCA score: 11).

Conclusions: Our patients showed very different post-HD plasma-to-CSF gradients. Theoretically, the positive gradient in patient B would favor intradialytic brain swelling. Patient B showed impaired neurological testing results which are not related to patient’s pre-existing neurological conditions. We can only speculate if and to what extent trans-BBB water movements driven by dialytic urea dynamics may have impacted the patient’s cognitive functions. We believe that patient-specific levels of osmotic stress need to be considered when developing neuro-protective HD technologies.

Figure 1: Urea concentrations in plasma (black line) and CSF (red line) (left panel: patient A; right panel: patient B).

Funding: Commercial Support - Renal Research Institute

Underline represents presenting author.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO0931
High-Throughput Analysis of Changes in Protein Biomarkers During Hemodialysis
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Background: The impact of hemodialysis on the concentration of circulating protein biomarkers remains unclear. Biomarkers may decrease in concentration due to filter adsorption, diffusive clearance, or convective clearance, while others may increase in concentration due to production and secretion or intracellular release. Ultrafiltration of water is also expected to increase biomarker concentration. We sought to evaluate the impact of hemodialysis on 1,163 protein biomarkers in a high-throughput fashion.

Methods: A nested cohort of 44 patients (25 male, 19 female) including 29 with intradialytic hypotension and 15 without were selected from the prospective Hemodialysis Outcomes and Symptoms assessment (HOST) cohort. Intradialytic hypotension was stringently defined as a 60 mmHg drop in systolic blood pressure or a nadir systolic blood pressure of less than 70 mmHg during hemodialysis treatment. All hemodialysis treatments were done using the same hemodialysis filter type. 1,163 unique biomarkers were measured in each patient before and after a hemodialysis session using the Olink proximity extension assay (www.olink.com). Paired sample t-tests were used to compare pre- and post-dialysis concentrations with a Bonferroni-corrected significance threshold (P < 5 x 10^-6).

Results: 54 biomarkers (5%) significantly increased during hemodialysis treatment, while 243 (24%) significantly decreased. Change in biomarker concentration was significantly correlated with biomarker molecular weight (r = 0.37, P = 2.8 x 10^-10), isoelectric point (r = -0.26, P = 6.4 x 10^-4), and pre-dialysis concentration (r = -0.21, P = 3.0 x 10^-4). There was a significant enrichment of cardiovascular biomarkers in the top 20 biomarkers associated with a drop in systolic blood pressure (P = 2.8 x 10^-7), including Kidney Injury Molecule 1 (KIM1, P = 0.005).

Conclusions: Hemodialysis is associated with significant changes in protein biomarker concentrations related to protein properties and clinical events during treatment. These changes are measurable on a high-throughput platform. Further high-throughput biomarker studies could assess dialysis adequacy, test biomarker-symptom associations, and improve risk prognostication.

Funding: Private Foundation Support

PO0932
Feasibility of Allo-Hemodialysis: First Experience from Porcine Studies
Xin Wang,1 Amrish U. Patel,2 Anil K. Gothi,3 Dejan Nikolic,4 Alexander Heide,5 Jianning Dong,1 Hao Zhang,6 Vaibhav Maheshwari,7 Nadja Grobe,8 K S Nayak,8 Peter Kottan,9 1 Renal Research Institute, New York, NY; 2Vivo Bio Tech Ltd, Hyderabad, India; 3Fresenius Medical Care Shanghai Co Ltd, Shanghai, China; 4Icahn School of Medicine at Mount Sinai, New York, NY; 5Vijivini Hospital, Hyderabad, India; 6Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany.

Background: Annually, millions of kidney patients, predominantly in low and low-middle income countries, die prematurely because of unavailability of affordable kidney replacement therapy. We previously demonstrated through mathematical modeling and bench testing the feasibility of alloHD, an alternative low-cost hemodialysis treatment approach where the blood of a kidney failure patient flows counter-current to that of a healthy donor (“buddy”) through a dialyzer. Herein we report first results from an alloHD feasibility study in a porcine model. We aimed to specifically address questions around hemolysis and coagulation of the dialysate compartment.

Methods: Ethics protocol was approved by Committee for the Purpose of Control and Supervision of Experiments on Animals, India. Under general anesthesia, healthy male female white Yorkshire pigs of 30 to 80 kg with central venous catheter as vascular access were dialyzed 1-3x weekly for 2-4 hours. Ultrafiltration volume goals were set between 0 and 1000 mL. “Patient” and “buddy” pigs were connected to the dialysate and blood compartments, respectively, of a Nipro Cellenta 171 (Fig. 1). Pigs were anticoagulated with 5000 IU heparin per hour. Pre- and post-treatment blood samples were collected for biochemical measurements.

Results: We successfully completed 10 alloHD sessions. No coagulation was observed. Visual inspection of plasma samples indicated no signs of hemolysis. This was further corroborated by measurements of lactate dehydrogenase and haptoglobin, which were available in seven experiments (Fig. 2).

Conclusions: We found no indication of hemolysis and dialysate compartment coagulation in our experiments. Upcoming studies in a porcine renal failure model will address in vivo solute clearances by alloHD.

Funding: Commercial Support - Renal Research Institute

PO0933
Can Plasma Filters Be Reused for Plasmapheresis in Resource-Poor Settings? Experience from a Tertiary Care Hospital
Priti Meena, Sandip Panda, Rishita Mondal, Swati Das. All India Institute of Medical Sciences - Bhubaneswar, Bhubaneswar, India.

Background: Therapeutic plasma exchange (TPE) is used in the management of various life-threatening illnesses. It is widely performed by nephrologists, intensivists, pathologists, or experts of transfusion medicine worldwide. However, the costs of TPE sessions are exceedingly high and it has a huge impact on patients’ financial burden. Most of the patients cannot afford such a high-cost treatment. Herein, we investigated the outcomes of reuse of plasma filters in TPE for several occasions

Methods: This was an ambidirectional study that included retrospective analysis of patients receiving TPE from January 1, 2021, to December 31, 2020, whereas the patients receiving TPE from January 1, 2021, to April 30, 2021, were prospectively analysed. The procedure was performed in our hospital’s dialysis unit. Formulation of 4% peracetic acid and 24% hydrogen peroxide acid with RO water was used for reprocessing. Fresenius Plasma Flux P2 (0.6 m2) was used in the study. Clinical outcomes, risks, and cost-benefit were evaluated and compared between the plasma filter reuse group (GP-1) and no reuse group (GP-2).

Results: 46 patients were included in the study. 26 patients were in the Plasma filter reuse group. 122 and 119 TPE sessions were performed in GP-1 and GP-2 respectively. A total of 58 plasma filters were used in GP-1. In six patients single plasma filter was used on 3 occasions whereas, it was used for 2 occasions in other patients. The most common indication for TPE in both groups was Guillain barre syndrome. The rates of clinical improvement in disorders for which the TPE were performed were similar in both GP-1 and GP-2 (88 % vs 90%, p=0.4). None of the patients in either group had clotting of plasma filter, any allergic reaction, or increased bleeding risk. No higher chances of sepsis were noticed in GP-1 (P=0.08). No difference in patient survival was noticed between the two groups (97% vs 96%, p=0.5). The cost of overall treatment was 2.5 times higher in GP-2, (P=0.003).

Conclusions: Reuse of plasma-filter is a safe and effective method for cost minimization in patients requiring TPE. This method can effectively be utilized in resource-poor settings without any increased risk of adverse effects

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO0934
A Forgotten Technique of RRT for Correction of Severe Hypotension in CKD: Case Report
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Introduction: Patients with chronic kidney disease (CKD) present electrolyte disorders. This represents a challenge when hypotension is below 125 mmol/L, associated with any criteria for urgent renal replacement therapy (RRT) with conventional hemodialysis because of higher risk of over correction above the security threshold of 10 mmol/L/day and osmotic demyelination syndrome.

Case Description: A 49-year-old Guatemalan female with history of 15 days of edema and slurred speech. Only history of T2DM. Was brought to the ER with BP 100/80 mmHg and anaerusa. Initial laboratory tests: negative COVID-19Ag, Cr 5.12 mg/dL, (previous 2mg/dL) BUN 105mg/dL, glucose 156mg/dL, Na 108mmol/L, K 5.2mmol/L, Cl 70mmol/L, SO4 224mmol/L, pCO2 35mmol/kg, UNa 28mmol/L. Because of neurologic symptoms, received a 150ml bolus of 3% saline twice with a rise to 112mmol/L. After the bolus, we initiated a 24-hour infusion with 3% hypotonic solution reaching a rise of Na up to 119mmol/L in 48 hours, but because of persistence of neurologic symptoms plus fluid overload >10% of body weight and hyperkalemia, we initiated RRT. In the absence of CRRT or CVVH we planned a conventional HD with blood flow of 100mL/min, dialysate flow 600mL/min, dialysate Na 130mmol/L (the lowest Na possible) and 3 hours duration. After the first session had neurologic and edema improvement. After two sessions with an interdialytic period of 48 hours, Na control of 122mmol/L and 132mmol/L respectively with resolution of uremic syndrome. Later was diagnosed with hospital-acquired pneumonia receiving antibiotic treatment for 14 days and was discharged home with ambulatory HD.

Discussion: In undeveloped countries where the access to CRRT or CVVH is unavailable, conventional modalities can be used with low blood flows and modification of the dialysate Na to a minimum (130mmol/L) offering a safe option to Na correction for patients with severe hypotension and any other HD criteria.

PO0936
Green Hemodialysis: Is It Really Possible to Save Water and Plastic Without Affecting the Quality of the Treatment? Ismael A. Gómez Ruiz, Geovana Martin-Alemalhy, Juan M. Ardavin Iruarte, Rossana Olmedo Ocampo, Santa Carmen Médica Santa Carmen, Ciudad de México, Mexico.

Background: Hemodialysis (HD) is essential for the preservation of life in many patients but represents a complex issue in ecology producing a large waste load that affects the environment. Sustainable waste management policies are scarce. The aim of the present study was to show the particular water and plastic savings in a mexican HD center that practices the reuse of dialyzers and reject water (RW) without affecting the quality of care provided for patients.

Methods: Prospective cohort study performed between January and May 2021 in a HD center with 90 patients (AK 98 Baxter®). HD center has 15 employees, 5 bathrooms and 12 sinks. Volumes of produced and reused RW were measured by flow meters. A detailed analysis of the residual biochemical content of RW was performed. The weight of plastic waste was compared between patients with reused membranes and patients without reusing the membranes. Finally, to evaluate the quality of the HD treatment in reused dialyzers (1-12 reuses), the difference between 5 monthly measurements of the spKt/V was determined using a repeated measure ANOVA considering a p>0.05 for no difference.

Results: During the study period 4158 HD sessions were provided, 394 m3 of RW were produced, 312 m3 (79%) were reused for all center sanitation purposes. Analysis of the residual biochemical content of RW is shown in Table 1. A total of 1902 HD sessions were performed with reused dialyzers. With each dialyzer reuse (Revaclear Baxter®) 0.88 lbs of plastic waste was spared. This translates into 1.53 tons less waste. No adverse effects were observed. No statistical significance difference was observed in single pool Kt/V between treatments with reused filters.

Conclusions: These results suggest that reuse of RW in the sanitation of the centers and dialyzer reuse resulted in significant savings in water and plastic without affecting the quality of treatment received by patients.

Table 1: Analysis of RW compared with US Environmental Protection Agency (EPA) and for the Association for the Advancement of Medical Instrumentation (AAMI) standards

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control-RW</th>
<th>RW EPA standard</th>
<th>AAMI standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum mg/dL</td>
<td>&lt;0.1</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Arsenic mg/dL</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Barium ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Uranium ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cadmium ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium mmol/L</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Chromium ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Copper mmol/L</td>
<td>22</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Cobalt ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Magnesium mmol/L</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mercury ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Manganese mmol/L</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Lead ppm</td>
<td>&lt;10</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Nickel ppm</td>
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<td>Selenium ppm</td>
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<td>Vanadium ppm</td>
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<tr>
<td>Cadmium ppm</td>
<td>&lt;10</td>
<td>0.1</td>
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</table>

PO0935
Single-Bolus Tinzaparin Anticoagulation in Extended Hemodialysis Sessions: A Feasibility Study
Benoit Harvey,1 Simon Léger,2 Naoul Elfoutouh,3 Michel Vallette,3 Louis-Philippe Laurin,2 Annie-Claire Nadeau-Fredette,3 Université de Montréal, Montreal, QC, Canada; Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.

Background: Few studies have assessed the use of low-molecular weight heparins for anticoagulation during extended hemodialysis (HD) sessions. This study aimed to evaluate the safety and efficacy of tinzaparin for anticoagulation of the extracorporeal circuit and dialyzer in extended, 8-hour, sessions.

Methods: This single-center study included all patients who underwent a single in-centre 8-hour session as part of their nocturnal home HD training between 2009 and 2020. Tinzaparin was delivered as a single bolus injection at time 0 with dosing based on the patient’s weight and doubling of standard 4-hour session dose. Tinzaparin safety effects were observed. No statistical significance difference was observed in single pool Kt/V between treatments with reused filters.

Conclusions: These results suggest that reuse of RW in the sanitation of the centers and dialyzer reuse resulted in significant savings in water and plastic without affecting the quality of treatment received by patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

318
Targeted Alteplase Administration to Improve Hemodialysis Catheter Patency: A Quality Improvement Pilot Study
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Background: Catheter dysfunction (CD) is a frequent complication during the provision of hemodialysis. Thrombolytic agents (i.e. alteplase) are the mainstay for resolving CD, however, alteplase usage has increased 16% (~$440,000CD) annually in the Alberta Kidney Care South program without improved patient or dialysis outcomes. We assessed the implementation of a protocolized algorithm to reduce alteplase usage.

Methods: In this pilot quality improvement study, we designed an algorithm where CD was treated with high-dose (2mg) alteplase therapy to the problematic lumen only, after meeting pre-specified criteria (Fig 1). This protocol was implemented in a satellite hemodialysis unit (~110 patients) from Jan 2021 to Mar 2021. The baseline comparison period was Jan 2020 to Dec 2020 when CD was treated with low-dose 1mg/lumen alteplase. Outcome measures included total alteplase usage, changes in Kt/V, recirculation, clearance, line interventions and hospitalization rates. Statistical analysis was completed using Mann-Whitney and Z-score calculations.

Results: Sixty-nine alteplase administrations occurred over the two-month period, versus 438 in the baseline period. Patients in the 2mg group were more likely to achieve an increase in Kt/V of at least 10% in the next dialysis session (34.7% vs 28.9% p=0.04). Otherwise the 2mg alteplase with our protocol was not inferior to baseline with respect to blood flow rate processed (26.1% vs 20.1% p=0.13) and average clearance (37.7% vs 28.5% p=0.37). A 12% decrease (88 vs 100mg/mo p=0.05) in alteplase use was observed with no differences in frequency of hospitalizations (8% vs 5.9% p=0.39) or line interventions (12.3% vs 7.3% p=0.20).

Conclusions: Our protocol with 2mg alteplase therapy to the problematic lumen was not inferior with respect to patient outcomes compared to baseline practices and resulted in lower alteplase use. An expanded multi-center prospective study is underway to further assess the broader applicability of these findings.

Implement alteplase administration protocol.

The Effect of Predilution Online Hemodiafiltration on Body Composition, Nutritional Status, and Mortality
Sannoo Miziari,1 Yoshiko Nishizawa,2 Aiko Okubo,3,4 Toshiaki Doi,5 Kazumi Yamashita,1 Kenichiro Shigemoto,3 Koji Usui,3 Michiko Arita,1 Takayuki Naito,1 Shigehiro Doi,2 Takao Manaki,3 Iryo Higai Ichiyokai Harada Byoin, Hiroshima, Japan; 2Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; 3Ichiyokai East Clinic, Hiroshima, Japan; 4Ichiyokai Yokogawa Clinic, Hiroshima, Japan; 5Hiroshima Daigaku Byoin, Hiroshima, Japan.

Background: We evaluated the effect of predilution online hemodiafiltration (HDF) on body composition, nutritional status and all-cause and cardiovascular (CV) mortality in maintenance dialysis patients.

Methods: All subjects (n=215) had blood flow rate of ≥200 mL/min and underwent HDF with a convective volume of 40 L/session or hemodialysis (HD), 4h/session, 3 times/week. Predialysis clinical data and same day postdialysis body composition parameters were subjected to machine learning methods to predict intradialytic SAS, as quantified by the ODD value and the SAS classification by the American Sleep Disorders Association.

Results: We examine intradialytic SAS severity in 16 patients (age of 54±11 years, 63% males, 39% Black) with arteriovenous vascular access. Mean SaO2 was 94.3±2.1%. Figure 1A shows a typical SaO2 annotated with the SAS intensity assessed by ODD. Two calculated metrics are plotted in Figs. 1C-D. The results reveal dynamic characteristic patterns of SAS with differential severity scores during HD. Figures 1E-G show the ROC for the classifiers when considering episodes of at least mild, moderate, or severe SAS, respectively. The maximum AUC is 0.93 for severe SAS episodes.

Conclusions: Our analysis suggests that entropy and recurrent-based quantifiers could be used as predictive indicators of intradialytic SAS. However, further studies are needed to assess their relationships to clinical outcomes.

Leveraging Technology and Innovation to Predict Events and Improve Dialysis Delivery

DENALI, a Phase 3b Multicenter, Open-Label Single-Arm Study of Roxadustat: Operational Learnings Within US Dialysis Organizations
Arnold L. Silva,1 Gopal Saha,2 Jeffrey L. Hymes,3 Lynda Szczecz,2 Yemisi Oluwatotin,2 Zhiqun Gong,2 Kenny Cooper,3 John W. Larkin,1 Boise Kidney & Hypertension Institute, Meridian, ID; 2FibroGen Inc, San Francisco, CA; 3Fresenius Medical Care North America Nashville, Nashville, TN; 4AstraZeneca, Wilmington, DE; 5Fresenius Medical Care North America, Waltham, MA.

Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor that promotes erythropoiesis and improves iron availability in patients with anemia of chronic kidney disease (CKD). This trial aims to provide practical data on roxadustat use in dialysis patients with anemia via a semi- pragmatic evaluation of introduction into providers’ practices (Fresenius Medical Care).
Methods: This open-label, single-arm study assesses the efficacy and safety of roxadustat in correcting/maintaining hemoglobin (Hb) in patients with CKD-related anemia receiving in-center hemodialysis at nine US sites (NCT04410198). Initial roxadustat dose is weight-based (erythropoiesis-stimulating agent [ESA]- naïve patients) or guided by an ESA dose-conversion algorithm (ESA patients), in this trial targeting Hb=11±1 g/dL. Roxadustat dose is titrated every 4 weeks based on Hb level or rate of change, with 24-week treatment duration and up to 1-year extension. Efficacy is assessed by change from baseline in Hb and proportion of patients achieving mean Hb ≥10 g/dL averaged over weeks 16-24. Exploratory endpoints include time to first red blood cell transfusion, proportion of patients achieving mean Hb ≥10 g/dL in first 8 weeks, intravenous use, and dosing adherence. Safety endpoints include treatment-emergent adverse events (AE), with COVID-19 positivity an AE of special interest.

Results: This ongoing trial was successfully initiated and enrolled (n=203) during the COVID-19 pandemic, with modifications for home dialysis. Baseline characteristics appear representative of the US dialysis population (Table).

Conclusions: This trial adds to phase 3 studies of roxadustat by evaluating its use in treating anemia of CKD in home/in-center dialysis patients during the COVID-19 pandemic, while providing a view into operationalization and ease of real-world use. Full study results will be presented.

Funding: Commercial Support - FibroGen and AstraZeneca

Table: Key Baseline Characteristics in DENALI Patient Population.

PO0942
Validation of Urea Removal in Novel Sorbent Dialysis System

Background: The Diallyt Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aim: To assess urea mass removal during a simulated dialysis utilizing a novel sorbent filter.

Methods: Nine simulated dialysis sessions were conducted utilizing between 50L and 125L volumes of dialysate circulated at approx. 400 mL/min & 37°C through a sorbent cartridge with a standard dialysate. (Table 1) It is expected that with each pass through the filter the dialysate urea mass will decline. The experiment is continued until breakthrough occurs or the infrusate outlet reaches 10 ppm of NH3. A solution containing K2, Ca and Mg salts were constantly infused to replenish electrolytes lost in each pass. Another solution was infused at a variable rate as determined by conductivity to maintain Na Balance.

Results: The results are provided in table 1. The average URR was 63.8 % ranging from 53.3 to 87.0 %. The average starting HUN was 48.2 mg/dL and the average ending HUN was 16.8 mg/dL.

Conclusions: The initial experiments using a sorbent filter demonstrate a URR of near 65 is feasible. Future design changes will be scaled to handle larger amounts of urea and provide acceptable clearances.

Funding: Commercial Support - Diallyt Inc

Table 1:

PO0943
Effect of Hemodialysis on Amyloid-β in Cerebrospinal Fluid and Plasma
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Background: Hemodialysis (HD) can reduce amyloid-β(Aβ) species in whole-body circulation by 30 to 50%. Due to the dynamic exchange of Aβ between the brain and the blood, we hypothesized that HD might lower Aβ levels in the cerebrospinal fluid (CSF).

Methods: In a dialysis network with over 160,000 patients, we identified three maintenance HD patients (age 36±9 years) with ventriculo-peritoneal (VP) shunts who were subsequently recruited for this IRB-approved research study. Study subjects were dialedyzed on Monday, Wednesday, and Friday. Plasma samples were collected at 6 timepoints during the 3 HD sessions. One subject was withdrawn over safety concern related to the VP shunt tap procedure. Two subjects further underwent VP shunt taps for CSF sample collection before and after the Wednesday and Friday HD sessions, and once on interdialytic days (Tuesday, Thursday). Aβ1-42 and Aβ1-40 were quantified by Neuro 3-Plex SIMOA assays (Quanterix, MA, USA).

Results: HD effectively reduced plasma Aβ1-42 by 41% and Aβ1-40 by 34% (Fig 1a and 1b, p < 0.01). In CSF, levels of Aβ increased after Wednesday HD sessions in subject 1 (Aβ1-42: 4.2-fold, Aβ1-40: 5.5-fold) and subject 2 (Aβ1-42 and Aβ1-40: 1.06-fold), while Aβ1-40 decreased after Friday HD sessions in both subject 1 (Aβ1-42: 0.1-fold, Aβ1-40: 0.7-fold) and 2 (Aβ1-40: 0.7-fold, Aβ1-40: 0.7-fold) shown in Figure 1c–f.

Conclusions: This is the first report of Aβ dynamics in the CSF and plasma of HD patients. While plasma levels were in similar ranges, we found high inter-individual variations of CSF levels. Different plasma-to-CSF ratios after HD may reflect individual brain Aβ pools that are accessed by HD. We corroborate previous reports demonstrating the removal of Aβ from the blood compartment by HD.
**PO0944**

**Circulating Microbiome and Cardiovascular Death in Patients with ESRD**

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**Background:** Patients with end-stage renal disease (ESRD) suffer from disproportionately high cardiovascular (CV) mortality. Accumulating evidence suggests a role for the circulating microbiome (CM) in the pathogenesis of CV disease; however, little is known about its association with premature CV mortality in ESRD.

**Methods:** In a pilot case-control study of 17 hemodialysis (HD) patients who died of a CV event and 17 matched HD controls who remained alive during a median follow-up period of 2.0 years, we compared the levels and composition of CM, including Bacteria, Archaea, and Fungi in serum samples by quantitative PCR and 16S or Internal Transcribed Spacer (ITS) ribosomal RNA (rRNA) sequencing, respectively. Association of the CM with CV death were examined using multivariable conditional logistic regression.

**Results:** 16S and ITS rRNA was detectable in all (except 3 for ITS) examined patients’ serum samples. Despite no significant difference in 16S rRNA levels and diversity between cases and controls, taxonomic analysis demonstrated differential community membership between groups, with significantly greater Actinobacteria and less Proteobacteria observed in cases than controls at the phylum level. At the genus level, Staphylococcus was numerically higher in cases than in controls, albeit not significantly.

**Conclusions:** Alterations of the CM may be associated with a higher risk of premature CV mortality in ESRD patients. Supported by NIDDK.

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**PO0945**

**Dysregulation of Fibrinolytic Process Contributes to the Thrombotic and Bleeding Complications in ESRD Patients**

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**Background:** End stage renal disease (ESRD) is a complex syndrome involving both cellular and humoral mechanisms. Both thrombotic and bleeding complications are observed which may result in cardiovascular and cerebrovascular adverse outcomes. Fibrinolytic system placed an important role in the regulation of hemostatic process. A comprehensive profiling of the components of fibrinolytic process may provide additional understanding of the bleeding and thrombotic complications in ESRD.

**Methods:** Citrated whole blood samples were collected from a cohort of ESRD patients (n=95). Normal citrated plasmas were obtained from healthy male and female individuals. These samples were analyzed for prothrombin time (PT), activated partial thromboplastin time (aPTT), prothrombinase-induced clotting time (PicT) and thrombin time (TT) using clot based technique. Fibrinolytic parameters such as urinokinase type plasminogen activator (uPA), plasminogen activator inhibitor-1 antigen (PAI-1), and D-Dimer were measured by using ELISA method. Functional PAI-1 was measured by using an amyodylthactic method. All results were compiled as group means ± SEM and respective ratios were calculated.

**Results:** All of the clotting results showed varying levels of elevated values in comparison to normal plasma. uPA levels showed wide variations and were increased (1.6 fold). D-Dimer was markedly increased in the ESRD patients (11.53 fold). Both functional (1.2 fold) and antigenic (3.07 fold) levels of PAI-1 were increased. Interestingly, the PAI-1 antigen levels was much higher in contrast to the functional levels suggesting a progressive consumption of this mediator.

**Conclusions:** These results suggest that the overall hemostatic system in ESRD patients is dysregulated due to the imbalance of the inhibitors such as PAI-1. The persistent activation of fibrinolysis is due to the increase production of uPA which facilitates endogenous fibrinolysis resulting in the elevation of D-Dimer. The generation of fibrinolytic enzymes results in increased fibrin/fibrinogen degradation products which may contribute to the observed intrinsinc and extrinsic coagulation defects as measured by the prolongation of PT and aPTT. Monitoring of fibrinolytic parameters along with clotting test may be helpful in the risk stratification and prediction of adverse outcomes in ESRD patients.

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**PO0946**

**Successful Treatment of Systemic Calciumis in a Teenager on Hemodialysis**

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**Introduction:** Systemic calcinosiis is rare in pediatric ESKD patients compared to adults. The subcutaneous tissues are most frequently involved. We present teenager in whom calcinosiis was detected incidentally on chest radiograph, and review its successful treatment.

**Case Description:** A 15 yo anuric female who had received hemodialysis(HD) for 18 months after renal transplant failure, was treated for progressive respiratory distress in the ICU. Significant history included osteoporosis, hypertensive cardiomyopathy, and renal failure since age 1. Chest-XR revealed bilateral pulmonary infiltrates and calcified lesions. Thoracic CT scan demonstrated calcified tracheal and bronchial cartilage rings. Flexible bronchoscopy revealed diffuse white/grey nodules throughout the wall of tracheobronchial tree. All cultures were negative. When notified of the finding of calcifications on CT scan, patient’s mother also asked about the firm nodules in the space between patient’s fingers. Dialytic phosphate (P) clearance, and non-calcium(Ca), non-aluminum(Al) based binder use were maximized, using sevelamer and lanthanum carbonate. Sodium thiosulfate and etalcalcetide were given iv post each dialysis. Dialysate Ca varied between 1.60-2.53 mg/dL, to avoid hypocalcemic stimulation of PTH and high CaXP. Lanthanum was discontinued after 3 months, once P levels declined. Other therapies were continued for 10 months; with monthly dose adjustment. PTH level decreased and P levels normalized. Etalcalcitide was reduced to maintain normal Ca level. After 10 months, is panimidoste was initiated to prevent further demineralization. This led to transient marked elevation in PTH. Combined therapies led to resolution of calcinosiis. However, tracheobronchial calcifications have not been reassessed, since neither chest imaging nor bronchoscopy have been clinically indicated.

**Discussion:** Calcinosiis is uncommon, yet treatable condition in pediatric dialysis patients. Combined use of old and new therapies was successful. Reversed side effects of therapies affects aging. Ectalcalcitide often causes hypocalcemia. Thiosulfate use is associated with nausea. Lanthamum is an effective metal Ca binder, but prolonged use may lead to accumulation and systemic deposition. The emergence of new P binders: ferric citrate, sucroferric oxyhydroxide, and bixalomer will offer exciting new treatment options.
Severe Thrombocytopenia due to Electron-Beam Sterilized Polysulfone Dialyzer Membrane Reaction

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Introduction: We describe a case of severe thrombocytopenia due to reaction with an electron-beam sterilized polysulfone (PS) membrane. This phenomenon has been previously described but is rarely reported. E-beam sterilized PS membranes are classically more biocompatible than cellulose-based membranes but adverse reactions may occur as demonstrated in our case.

Case Description: A 74 y.o. woman with CKD Stage 4 and secondary hyperparathyroidism presented for evaluation of generalized weakness, anorexia, and weight loss. Her past medical history included gout, short bowel syndrome following prior bowel resection and osteoporosis. Home medications were allopurinol, calcitriol, gabapentin, fluoxetine, and mirtazapine. She was started on hemodialysis (HD) for suspected progression to ESRD. She developed progressive thrombocytopenia (Figure 1) that was more following HD1 with improvements on non-HD days. Evaluation of usual culprits of thrombocytopenia was unrevealing. Reaction to the polysulfone filter was suspected and she was switched to a cellulose-based filter with resolution of her thrombocytopenia. She was dialyzed with a PS membrane on HD20 as proof of concept with recurrent thrombocytopenia following HD2. She was dialyzed with cellulose-based filter thereafter with no further thrombocytopenia.

Discussion: We describe a case of PS-membrane induced thrombocytopenia. It is hypothesized that e-beam radiation may affect membrane integrity or structure, or produce intermediary products which may cause platelet activation, aggregation, and adhesion and therefore thrombocytopenia. This entity should be considered in the differential diagnosis of patients undergoing HD who develop thrombocytopenia. Early recognition may reduce incidence of bleeding and need for blood products in these patients.

The frequency of treatments reported on a Saturday was only 92% of that on a Tuesday. The frequency of by-pass (or alerts) was not related to day of the week.

Conclusions: The variation in frequency of treatment by the day of week suggests “social” causes — i.e. a “night off” is more frequent on the weekend. Either some form of treatment event or alert is present in a substantial minority of APD sessions. The relationship of these events with technique survival is important, but not yet known. In this time linked data will allow examination of events recorded during treatment with patient outcomes.

Funding: Commercial Support - Baxter Healthcare

PO0950
Feasibility of a Staff-Assisted Peritoneal Dialysis Program in the United States: Results of a Pilot Study

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Background: Staff-assistance can support patients to utilize peritoneal dialysis (PD) and is available in many countries but not in the US. We report on the initial experience from a feasibility study for staff-assisted PD in the US.

Methods: An assisted PD program was initiated at one home dialysis center in Aug 2020, and expanded to a total of 6 centers by Feb 2021. Home assistance by non-registered nurse staff was offered to patients with barriers to self-care with the aim to support patients and families to become independent from staff assistance.

Results: Participating centers referred 33 patients (range: 0 – 16 referrals) (16 referrals were cancelled [admission from HD to the home program cancelled (3 referrals), treatment not tolerated (2), patient preferred to continue HD (5), death (3)]). Of the 17 referred, 15 patients started staff assistance (less than 3 months of assistance (8), and death (1)), 3 referrals are pending, and 14 patients received staff assistance at home. Of those who received assistance, median age was 72 years (34-87 years), and 8 were new to PD. Indications included: physical weakness (10 patients), cognitive difficulties, and psychosocial issues (7). One prevalent PD patient required assistance following a PD peritonitis episode. Anxiety and lack of confidence were common among referred patients. Staff member attending the patient’s home assisted with removal and replacement of PD bags (5 patients), machine setup (9), dressing of exit site (7), checking the blood pressure (2), and other requests (8) such as documentation. Assisting staff worked with patients to build problem-solving skills, gain self-confidence, and arrange a safer home environment. Median length of time on the service was 17 [IQR: 6 – 23, range: 2 – 49 days], and median number of visits was 15 (range: 4 – 38, IQR: 5 – 26) visits/patient. Median revisit duration was 45 (range: 15 – 90) minutes. Seven of the patients who finished are more than 90 days after starting assistance. Six of them remain on PD and one patient transferred to HD.

Conclusions: Staff-assistance can support patient transition to, and maintenance on, PD. Such programs are operationally feasible with non-RN staff in the US and should be supported by Medicare and regulatory agencies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

322
PO0951

Increasing the Prevalent Peritoneal Dialysis Patient Population Can Be Challenging

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Background: Peritoneal dialysis (PD) can provide better quality of life for patients requiring renal replacement therapy compared to in centre dialysis. It can be challenging to increase prevalent patient population on PD after a certain number is reached. We did a retrospective analysis to assess the turnover of patients on PD over a 8 year period and to understand the reasons for a stagnant prevalent PD population in the renal unit in Royal Derby Hospital.

Methods: Electronic medical records were used to track the number of prevalent PD patients enrolled each year from 2009 to 2017. Reasons for stopping PD and duration of technique survival were noted. If technique failure resulted in conversion to haemodialysis, it was noted for more than 3 months, the cause of the failure was also noted. Patients who converted to HD for less than 3 months were excluded from the study.

Results: The number of patients starting (n=324) and dropping off PD (n=322) was similar for each year between 2013 to 2020. Modality switch to haemodialysis accounted for 40-60% of patients stopping PD, followed by death (15-30%) and patients receiving renal transplantation (10-35%). Modality switch to haemodialysis was primarily due to infection (60-80%), poor clearances and ultrafiltration failures (10-30%), social reasons (10-15%). Among patients who switched to HD due to an infection, peritonitis accounted for 75-85% of the cases followed by exit site and tunnel infections (15-25%).

Conclusion: Increasing the prevalent population on PD can be challenging even with a high incident PD population. Having mechanisms which prevent infections, early identification and treatment of infections may help increase prevalent PD population.

PO0952

Disparities in Kidney Care: Where Care Needs to Be Equal


Background: Disparities in kidney care are widespread and gaining more attention. This research focuses on care differences that existed between home hemodialysis (HHHD) and in-center hemodialysis (ICHD) patient from 2017 to 2020.

Methods: Using a HIPAA-compliant, online chart review tool, nephrologists submitted de-identified clinical and non-clinical demographic information beginning at the time of patient referral and concluding with details from the most recent visit. These data, from 2017 through 2020, were then merged with the physician demographic profile and attitudinal responses. The full data set of 4,062 patient charts submitted from 1,021 nephrologists was analyzed in SPSS.

Results: Given the efforts to promote home modalities, nephrologists are following status quo and continue to initiate new dialysis patients on in-center hemodialysis. Nephrologists' current patient loads consist of, on average, 5 HHHD patients and 9 ICHD patients. On average, they initiate one new patient on HHHD compared to 17 new ICHD patients per year. When comparing HHHD and ICHD patient charts there are substantial differences between the two patient types. ICHD patients tend to be Caucasian and from higher education and socioeconomic levels: 52% are Caucasian and 25% are African American, 37% have some college (14% have an advanced degree), and 67% are middle or upper class. Conversely, ICHD patients tend to be more diverse (40% are Caucasian, 40% are African American), less educated (24% have some college and 5% have an advanced degree) and from lower socioeconomic classes (44% are lower or lower-middle class). Further, 40% of patients on home modalities are employed part- or full-time, versus 18% of patients on ICHD. Insurance coverage – both at dialysis initiation and current – influence modality choice as well. Notably, 70% of patients on home modalities were followed prior to dialysis, whereas only 48% of patients on ICHD were followed pre-dialysis, and patients on home modalities are substantially more likely to be on the transplant list versus ICHD patients (62% versus 37%).

Conclusions: Disparities in care exist between patients receiving home hemodialysis versus in-center home hemodialysis. As kidney care continues to evolve, physicians will need to account for these differences in their treatment paradigms to ensure they provide comparable care across patients.

PO0953

Characteristics and Treatment Patterns of Dialysis Providers Randomly Assigned to the Medicare ESRD Treatment Choices Model

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Background: In January 2021, Medicare’s End-stage Renal Disease Treatment Choices (ETC) model randomly assigned 30% of US dialysis facilities to receive financial bonuses and penalties on the basis of their home dialysis use, waitlisting, and living-donor transplantation among their patients, compared with benchmarks from non-ETC-assigned facilities. We assessed whether sampling variance may influence ETC performance by comparing pre-ETC treatment use among ETC-assigned and non-assigned facilities.

Methods: We compared rates of transplantation (living and deceased donor transplantation) and home dialysis use (peritoneal dialysis, home hemodialysis) at 12 months among patients with incident kidney failure during July 2014-June 2018 in future ETC and non-ETC dialysis facilities (n=7527 facilities, n=192755 patients). In logistic regression models with region random effects and Bonferroni-adjusted robust standard errors, we assessed associations between ETC assignment and patient and facility characteristics (ownership, home dialysis offerings, staffing), patient case-mix (demographic, clinical, and insurance characteristics; mortality), and area-level socioeconomic status (e.g., median household income).

Results: Prior to ETC, patients in ETC-assigned facilities had 22% (0.71 pp) higher rates of living-donor transplant receipt (p<0.005), 24% (0.89 pp) higher rates of deceased-donor transplant receipt (p=0.001), and 9% (3.3 pp) lower mortality rates (p<0.001) at one year versus in non-assigned facilities. Rates of home dialysis use were similar for ETC-assigned and non-assigned facilities, 21% (2.0 pp) more likely to be owned by a small-for-profit chain and 16% (5.8 pp) more likely to be owned by the second largest dialysis organization (p=0.001). Adjusting for other factors, dialysis facilities were more likely to be ETC-assigned if their patients were younger and if they had a lower percentage of patients who were Hispanic (both p<0.001).

Conclusions: Due to sampling variance, ETC-assigned facilities may be disproportionately likely to receive bonuses (vs penalties) under the model, even if they do not increase home dialysis treatment and transplant receipt among their patients.

Funding: NIDDK Support

PO0954

Novel Transitional Care Unit Design Achieves >50% Home Dialysis Choice in Incident ESRD Patients


Background: In 1983 Eschbach reported that a 6 station Home Dialysis (HD) Orientation Unit at Northwest Kidney Center had a 62% success rate in incident ESRD pts choosing HD. The RV CARE study of intensive in center HD education during routine thrice weekly dialysis had 38% of pts chose HD. Satellite Dialysis found that with their Transitional Care Unit (TCU) 30 % of pts chose HD.

Methods: We designed a 6 station dedicated TCU staffed with the added benefit of its main teaching nurse having 4 years each of being a home hemodialysis (HHD) & peritoneal dialysis (PD) nurse coordinator. The unit contains 3 NxStage & 2 Liberty Select Peritoneal cyclers. Pts are dialyzed 4 times weekly on the Nxstage or eventually the cyclers. Additional support is given by dialysis nurses trained in HHD & PD as are the social worker and dietitian educators. Intensive education with a defined curricula in all forms of HD are given including shared decision making with families. A medical director highly skilled in HD therapies also re-enforces the education delivered by the entire team every week. All 67 of our pts starting dialysis since July 2020 received standard dialysis education with several phone or virtual education sessions from our outpatient CKD coordinator, description of the TCU, plus a home visit by one of our HD coordinators.

Results: Since July, 2020 67 pts have started ESRD therapy, with 35 choosing not to enter the TCU and 32 choosing the TCU. Only 7 of 35 pts received the standard way chose HD, 4 PD & 3 HHD but 17 TCU pts out of 32 chose HD, 10 HHD & 7 PD, 53%, p=004 compared to standard education. There were no significant differences in duration of nephrology followup, age, sex or causes of ESRD between the 2 groups.

Conclusions: We conclude the success of our TCU is due to the following: 1) Pre-ESRD education about the benefits of starting dialysis in a TCU & 2) Most importantly having a skilled and experienced home HD and PD nurse coordinator to be the main educator and pt champion for both HHD adn PD. 3) Utilizing a HD skilled medical doctor & social worker using shared decision making adds confirmatory education on the benefits of HD.

Funding: Clinical Revenue Support

PO0955

Home Hemodialysis with the Tablo System: The First 1000 Real-World Treatments

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Background: The Tablo® Hemodialysis System is an all in one, easy-to-learn device capable of achieving clearance goals in as little as three treatments per week. It features integrated water purification, on demand dialysate production and two-way wireless data transmission. Tablo obtained FDA clearance for home hemodialysis (HHD) in March 2020. Approval was based on a prospective, crossover trial (in-center and at dialysis) where Tablo successfully met all safety and effectiveness endpoints, reported high rates of treatment adherence and patient retention, with greatly reduced training time (NCT02460263). The objective is to report on the first 1,000 treatments performed on Tablo by patients at home in the real-world.

Methods: Incident and prevalent patients currently performing in-center dialysis, PD, or HHD were initiated on Tablo at participating Home Dialysis programs. Patients were initiated by facility nurses on the Tablo device prior to beginning treatments at home. Data on the first 1000 treatments was obtained wirelessly via Tablo's data platform along with corresponding patient training data.

Results: The first 1000 treatments occurred in 20 patients, with a mean follow-up duration of 3.4 months. Patient training on Tablo was completed over an average of 7.4 training sessions. Retention was 98% for patients initiating treatment on Tablo. Mean prescribed treatment time was 3.2 hours with a mean frequency of 3.7 treatments.
per week. Mean total UF per treatment was 1.9 L. Mean UF rate per treatment was 7.3 mL/kg/h. Treatment adherence was 93%, with 95% of treatments completing within 10% of prescribed time. The mean number of clinically significant alarms per treatment was 1.0 (± 3.0), with an average time to resolution of 10.7 (± 18.5) seconds.

**Conclusions:** Results from the Tablo IDE demonstrating reduced training time, increased treatment adherence, high treatment success rate and a low occurrence of treatment alarms are reproducible in the real world at a frequency of 3-4 treatments/week. This data supports that Tablo is capable of successfully achieving clinical goals while reducing the overall patient burden often associated with HHD.

**Funding:** Commercial Support - Outset Medical, Inc.

**Tablo Home Hemodialysis Data**

**PO0956**

**Recent Trends in Utilization of Home Dialysis Modalities, Overall and by Duration of ESKD**

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**Background:** The Executive Order on Advancing American Kidney Health and the End Stage Renal Disease Treatment Choices payment model have focused attention on increasing utilization of home dialysis. We assessed trends in home dialysis utilization between 2016 and 2021, including variability in trends among strata defined by duration of end stage kidney disease (ESKD).

**Methods:** We analyzed dialysis facility admission and discharge data extracted from the End Stage Renal Disease Quality Reporting System in May 2021. During the epidemiologic week of each year from 2016 to 2021, we identified patients undergoing maintenance dialysis at the beginning of the week. For each patient, we identified the current dialytic modality. We estimated trends in utilization of each modality, overall and by duration of ESKD at the beginning of the week (<2, ≥2, 4, 5-9, and ≥10 years).

**Results:** Between 2016 and 2021, home dialysis utilization increased from 11.5% to 14.3%, with the majority of growth occurring since the beginning of 2019 (figure). Concurrently, HHD utilization increased from 1.57% to 2.23%, whereas PD utilization increased from 10.0% to 12.0%. Among patients with ESKD duration <2 years, home dialysis utilization increased from 14.8% in 2016 to 20.0% in 2021, with >90% of utilization in this stratum due to PD. Among patients with ESKD duration 2-4 years, home dialysis utilization increased from 11.7% in 2016 to 13.7% in 2021. Among patients with ESKD duration ≥10 years, home dialysis utilization hovered around 9%, although HHD utilization reached a high of 3.65% in 2021, representing nearly 40% of home dialysis utilization in this stratum.

**Conclusions:** Growth of home dialysis utilization has accelerated since 2019, with greater absolute growth of PD and greater relative growth of HHD. Longer duration of ESKD is associated with lower utilization of PD, but higher utilization of HHD.

**Funding:** NIDDK Support

**PO0957**

**The Impact of Seasonality on Crash Starts and Home Dialysis Use**

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**Background:** The US has made a concerted effort to increase home dialysis use. Dialysis “crash starts,” when patients emergently initiate dialysis in the hospital, are a barrier to home dialysis because they often preclude successful planning. We studied whether the season of the year was associated with crash starts and with home dialysis use among incident patients with end-stage kidney disease (ESKD).

**Methods:** From the United States Renal Data System, we identified all adults with at least 30 days of continuous Medicare Parts A and B coverage initiating dialysis from 2007-2017. We identified home dialysis use and whether patients were hospitalized within 14 days prior to the first outpatient dialysis treatment (i.e., “crash start”). Using multivariable logistic regression, we studied the association between season, likelihood of crash start, and starting dialysis at home. We used a Cox model to study whether crash starts were associated with ever using home dialysis in the first year. We adjusted for demographics, comorbidities, facility and geographic characteristics, and year of dialysis start.

**Results:** After adjusting for confounders and year of dialysis start, patients were less likely to start dialysis in the winter versus the summer (OR: 0.86, 95% CI: 0.82, 0.90). Conversely, patients were more likely to “crash start” into dialysis in the winter versus the summer (OR: 1.14, 95% CI: 1.11, 1.17). Patients with a crash start were substantially more likely to initiate with home hemodialysis (OR: 0.16, 95% CI: 0.15, 0.16) and were less likely to ever use home dialysis in the first year (HR: 0.41, 95% CI: 0.40, 0.42).

We observed seasonal heterogeneity in the admission diagnoses. Hospitalizations due to pneumonia, myocardial infarction, and congestive heart failure were 1.6, 1.4, and 1.3 times more likely to occur in the winter versus the summer, respectively. Hospitalizations due to diabetes, complications of devices, and chronic kidney disease were 1.05, 1.08, and 1.08 times more likely to occur in the winter, respectively.

**Conclusions:** We observed more dialysis crash starts in the winter and a subsequent decrease in home dialysis use in the first year. Winter hospitalizations were more often associated with cardiovascular and pulmonary etiologies. Clinicians should remain vigilant that patients may be prone to crash starts in the winter and should accelerate dialysis planning accordingly.

**Funding:** NIDDK Support

**PO0958**

**Comorbidity Is Not Associated with Home Dialysis Choice**

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**Background:** Over the past 15 years the proportion of Dutch home dialysis patients has decreased markedly. In addition, the rate of home dialysis varies significantly among centers. It is unclear whether this is the result of increased comorbidity, other patient characteristics or because dialysis centers perceive barriers for home dialysis differently. Our aim was to investigate the association between comorbidity and home dialysis choice.

**Methods:** The DOMESTICO study is a multicenter retrospective cohort study on home dialysis and randomly selected in-center hemodialysis patients. Comorbidity data was collected of patients who started dialysis between 2012 and 2017, including those who had previously received dialysis or obtained a kidney transplant. Patients who stopped dialysis or died within 30 days were excluded. Comorbidity was assessed with the Charlson comorbidity index (CCI). Home dialysis was defined as any peritoneal dialysis or home hemodialysis treatment during follow-up. Patients were followed until kidney transplantation, wish to stop dialysis, death or study end on 1 January 2017. Multivariable logistic regression analysis was used to assess the association between comorbidity and home dialysis, with a mixed model approach to adjust for dependency of patients within dialysis centers and for other patient characteristics including age, sex, and body mass index (BMI).

**Results:** Of 1358 included patients, 46% were treated with home dialysis. A high comorbidity score (CCI ≥5) was associated with a lower probability to receive home dialysis compared to patients without comorbidities (unadjusted OR 0.74, 95% CI 0.54–1.00). After adjustments for patient characteristics including age and BMI, there was no association between comorbidity and home dialysis. Only obese patients (BMI ≥30 kg/m²) with comorbidities had a significant lower likelihood to receive home dialysis compared to obese patients without comorbidities (medium comorbidity score (CCI 1-4) adjusted OR 0.40, 95%CI 0.18–0.86 and high comorbidity score (CCI ≥5) adjusted OR 0.43, 95%CI 0.20–0.93).

**Conclusions:** Comorbidity is not associated with home dialysis, after adjustment for several confounding factors including age and BMI. Future studies should aim at unraveling the center-specific characteristics that play a role in dialysis treatment.

**Funding:** Commercial Support - Nierstichting/Dutch Kidney Foundation – non-profit organisation. Grant no: AZ4DP02.
Reducing Routine Bloodwork in Home Dialysis Patients: A Quality Improvement Initiative

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Background: There is a paucity of evidence for routine bloodwork frequency in maintenance dialysis patients to assess and manage complications such as anemia and mineral bone disease (MBD). Recent studies showed that decreasing the frequency in conventional in-center hemodialysis (ICHHD) patients had no negative impacts. Given the strain on lab services from the COVID-19 pandemic, Alberta Kidney Care-South (AKC-S) decreased the frequency of routine labs from monthly to every 2 months in home hemodialysis (HHHD) and peritoneal dialysis (PD) patients. We studied the effect of this change on patient outcomes.

Methods: We retrospectively compared prevalent home dialysis patients (>3 months) in AKC-S over two 6-month periods: a) Pre-pandemic May-Oct 2019 and b) Pandemic May-Oct 2020. Primary outcomes were number of routine bloodwork days and percentage of patients within target for anemia (hemoglobin, iron saturation) and MBD (calcium, phosphorus, parathyroid hormone). We also compared hospitalizations, mortality, technique failure (defined as transition to ICHD for >60 days), and cost.

Results: There were 366 home dialysis patients in 2019 (270 PD, 96 HHHD) and 400 in 2020 (296 PD, 104 HHHD). The number of routine bloodwork days decreased in 2020 compared to 2019 (p=0.01) (Fig 1). The proportion of patients who achieved anemia (33% vs 35%, p=0.44) and MBD (34% vs 28%, p=0.1) targets was similar. There was no difference in the number of hospitalizations (155 vs 141, p=0.34), deaths (13 vs 17, p=0.71) or technique failure (8% vs 5%, p=0.06). Projected cost savings were $102 per patient year from reduced labs.

Conclusions: AKC-S reduced the frequency of routine labs during the pandemic in home dialysis without negative consequences on patient biomarkers or outcomes. Our study suggests that bloodwork frequency in home dialysis patients may be safely reduced.

On-Demand Automated Peritoneal Dialysis Solution Generation

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Background: While automated peritoneal dialysis (APD) is an effective treatment for kidney failure, ordering, delivery and storage of supplies can be challenging. The APD Solution Generation System (SGS) allows for dialysate solution generation using tap water in a patient’s home with fewer supplies (Figure 1).

Methods: A 12-week single-arm, prospective, descriptive study was conducted with in-home APD patients. Patients were screened, trained and treated with the SGS. Endpoints included testing the final product against specifications for Dianeal and water purification ISO Standard 13959 and measuring PD adequacy. Adverse events and device deficiencies were collected.

Results: 22 patients were enrolled; 14 patients completed the study. Demographics are shown in Table 1. See Figure 1 for primary efficacy and safety endpoint results. All tested post-sterilization filter and final dialysis solution samples passed. Missing data for water purity attributed to only 56.9% of samples passing. Mean (SD) change from baseline for Kt/V was -0.15 (0.370). There were 2 peritonitis events (0.43 episodes per patient-year), 1 occurring in a patient with HIV. There were no safety signals.

Conclusions: The SGS has the technical capability to accurately and safely generate dialysate at the point of care, maximizes dialysis performance, and optimizes treatment protocol. Remote monitoring capability by SGS allows remote supervision and management, an efficient choice especially in Covid-19 times.
PO0962
Animal Trial of Sorbent Cartridge for Portable Artificial Kidney (PAK) In Vivo Maintenance Peritoneal Dialysis Using a Sorbent-Based PD Device in a Porcine Model
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**Background:** The NextKidney/Dialysis HD Sorbent Cartridge (SC) uses a novel type of sodium-neutral sorbent to regenerate spent dialysate for standard hemodialysis (HD) therapies. The SC is intended to be used with the NextKidney sorbent HD device, where it produces fully physiological dialysate meeting today’s industry standards. We tested the safety and efficacy of the sorbent system in a total failure kidney pig model. The animals were maintained exclusively on sorbent HD for up to 2 weeks.

**Methods:** Three highly uremic pigs (60–75Kg) underwent a total of 14 alternate-day, 4h sorbent HD therapy sessions. Total renal failure was induced via bilateral renal artery embolization (pig #1), or bilateral laparoscopic ligation of renal arteries (pigs #2 and 3). A palindromic catheter provided blood flow rates of 200 – 300mL/min. A hemoperfusion machine was used for the blood circuit, coupled with a prototype device controlling the dialysate circuit. Dialysate was continuously purified in the SC at a flow rate of 300 mL/min. Therapy efficacy and mass balances were calculated from blood and dialysate samples collected before and after the dialyzer at specific time points.

**Results:** The animals tolerated the therapies well. The incision site at the femoral artery and vein was noted during internal bleeding and loss of the animal. Fourteen 4hr dialyses were averaged to calculate toxin removal efficacy and mass balances. The average clearances for urea, creatinine and phosphorus were 139, 146 and 141mL/min, respectively. Dialysate sodium and bicarbonate concentrations remained within the permissible deviations of +/-5% and +/-25%, respectively.

**Conclusions:** The biocompatibility of the sorbent system has been confirmed in fourteen 4h HD therapies conducted on three highly uremic pigs. The sorbent system was able to maintain the highly uremic animals. There were no severe adverse events related to the sorbent HD therapy. We currently plan to proceed to a first-in-human trial to evaluate the safety and efficacy of the sorbent cartrige for human use.

**Funding:** Commercial Support - AWAK Technologies Pte Ltd and Neokidney B.V.

**Table:**

<table>
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<tr>
<th>Solutes</th>
<th>Scource</th>
<th>Scourcedialysate (mmol/L)</th>
<th>Regenerateddialysate (mmol/L)</th>
<th>Deviation (%)</th>
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<td>HESD</td>
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**Average Dialysate Concentrations**

PO0963
Thirty Days of Maintenance Peritoneal Dialysis Using a Sorbent-Based Automated Wearable Artificial Kidney (AWAK) PD Device in a Porcine Model
Manoj W. Foo,1 Hayi Huy,1 Edwina A. Brown,2 Sridhar Chirimarry,3 Marcin Pawlak,2 Siti N. Huda,1 Jason T. Lim,1 Sanjay Singh,1 Mandar Gori,1 Suressa B. Venkatary,1 Arsh Jain,4 Singapore General Hospital, Singapore, Singapore; 2Hammersmith Hospital, London, United Kingdom; 3AWAK Technologies Pte Ltd, Singapore, Singapore; 4Western University, London, ON, Canada.

**Background:** In sorbent-based PD, spent dialysate is processed and clean dialysate is re-introduced into the abdomen. Our aim was to determine if AWAK dialysis can maintain euvolemia and biochemistry for 30 days in a porcine model.

**Methods:** The study was conducted in a 5:6 nephrectomised pig (Sus Scrofa, male). Post nephrectomy, the animal was treated with CAPD (14 weeks) before commencing sorbent-based PD for 7 hour per day with initial fill of 2L 1.5% Dianeal for 30 consecutive days. Thereafter, the animal was maintained on standard of care (SOC) for 3 days (5x2L exchanges over 10 hour APD, with 1L last fill, 2.5% Dianeal).

**Results:** Stable serum concentration of toxins, electrolytes and inflammatory markers were noted during AWAK therapy (Table); with no significant change after switch to SOC. pH of regenerated dialysate was consistent with biocompatible solutions (figure 1) and appropriate change in ultrafiltration was observed in response to glucose infusion (figure 2).

**Conclusions:** AWAK PD therapy successfully treated a CKD animal model for 30 days, without adverse impact on volume status or clinical parameters. Future long-term human studies are needed for device enhancement.

**Funding:** Commercial Support - AWAK Technologies Pte Ltd

**PO0964**

**Smartphone Application to Assist Peritoneal Dialysis Patients for Timely Detection of Peritonitis**
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**Background:** Timely detection of peritonitis in patients undergoing peritoneal dialysis (PD) is critical to lower the risk of catheter loss, morbidity and mortality (Mufuucumaran, 2016). Current practice of screening potential peritonitis events at home relies on patients’ visual detection of turbid spent dialysate and symptoms recognition. To assist patients with the timely capture of a potential peritonitis episode, we developed a smartphone app, which uses light detection to quantify cloudiness and estimate white blood cell (WBC) count in PD effluent (PDE). The app uses the built-in light sensor and compares measurements taken from the ambient light (Lambient) and light through PD bags (Lbag) to estimate dialysate cloudiness. PDE samples were obtained as part of two IRB-approved clinical studies over a period of 6 months. Cloudiness of each sample was measured 3x with the app. Cloudiness (in %) was calculated as (1 - Lbag/Lambient) x 100. WBC were counted using a hematology analyzer (Horiba 80XL).

**Results:** Patients maintained a stable baseline cloudiness of 2.5% (Fig 1). A peritonitis episode (subject PDMET0002) increased the cloudiness to 40%, which is 32 percentage points over the patient’s peritonitis-free baseline. One suspected peritonitis sample (albeit WBC’s <100 cells/mL) showed slightly higher cloudiness than non-peritonitis samples (Fig 2).

**Conclusions:** Our smartphone app can distinguish peritonitis from normal PD samples. Smartphone-enabled detection of cloudiness in PDE samples using light transmission is possible and has the potential to easily monitor and diagnose patients at risk for peritonitis. Studies to define diagnostic performance in a large patient cohort are underway.

**Funding:** Commercial Support - Dialyss Pte Ltd and Neokidney B.V.
PO0965
Remote Monitoring of Patients with Automated Peritoneal Dialysis May Improve Clinical Outcomes: Analysis by Competing-Risk Regression Models
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Background: Current information technologies allow remote monitoring (RM) of patients on automatic peritoneal dialysis (APD) and the adoption of proactive behaviors to prevent complications and improve treatment quality. We analyzed the effect of RM-APD on survival and preventable complications through a controlled clinical trial.

Methods: In a two-branched cluster RCT, hospitals with >100 prevalent, >50 new patients per year, and >5 years APD experience were randomly assigned to perform RM-APD or conventional APD with equivalent APD-equipment in adults beginning APD. The primary outcome was a composite index (CI) of death, first adverse event (AE) or first hospitalization. Secondary outcomes were the same variables considered individually and for their specific causes. All-cause and cardiovascular disease (CVD) mortality risk and AEs were analyzed with competing-risk regression with transplantation as competing risk.

Results: Eleven hospitals per arm were included and 815 patients were followed-up by at least one year, 417 using RM-APD and 398 on APD. Patients in hospitals using APD reached earlier the CI as well as its individual components. Patients with APD as compared to RM-APD were older, more inflamed, and had higher all-cause and CVD mortality. In competing risk analysis, after adjusting for age, sex, presence of smoking, hypertension, CVD and diabetes, APD as compared with RM-APD associated with higher subdistribution hazard ratio (sHR) for all-cause mortality (sHR 1.79, 95%CI (1.15-2.81); p=0.01), CVD-related mortality (sHR 2.21, 95%CI (1.07-4.38); p=0.03) and AE (sHR 1.74, 95%CI (1.34-2.25); p=0.001).

Conclusions: Use of RM-APD may improve survival and prolong the time to first AE and hospitalization in comparison with APD, suggesting that RM-APD may improve clinical outcomes in APD patients.

Funding: Commercial Support - Baxter

PO0966
Peritoneal Dialysis Discontinuation: Trends and Risk Factors

Background: Increasing use of dialysis home modalities among ESRD patients is a Centers for Medicare and Medicaid Services priority. This can be accomplished by increasing use of home dialysis among incident patients or by reducing PD discontinuation.

Methods: We identified incident ESRD patients from 2008 to 2018 who received peritoneal dialysis in their third month of ESRD treatment. We used data from CROWNWeb and Medicare claims to determine the patient’s modality 1, 2, and 3 years after initiation of ESRD treatment. We summarize trends in share of incident PD patients who were treated with PD at each follow up and describe differences by patient and facility characteristics.

Results: From 2008 to 2017, approximately 70 percent of incident PD patients remained on PD after 1 year of dialysis, 50 percent after 2 years, and 30 percent after 3 years of dialysis (figure 1). Over these years the percentage of incident PD patients treated with PD after two years rose from 47.9 to 52.3 percent. The rate of two-year PD persistence has declined modestly since a peak of 53.1 percent in 2013. PD patients treated at DaVita facilities were more likely than those treated at FMC or independent facilities to remain on PD after two years. PD patients treated at facilities with a higher share of PD patients were more likely to remain on PD after two years. Among incident PD patients, the rate of peritonitis during the first year of dialysis declined from 33.5 to 21.7 between 2010 and 2018. Peritonitis was more common among dual eligible patients, Black and American Indian/Alaska Native patients, and overweight or obese patients.

Conclusions: Differences in PD discontinuation and peritonitis incidence across patient and facility subgroups represent opportunities for future quality improvement efforts.

Funding: Other U.S. Government Support
PO0968

Contemporary Incidence of Peritoneal Dialysis Attrition and Variability Therein Among Age Strata

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Background: With an increasing percentage of patients performing dialysis in the home setting, quality measurement systems should increase focus on home dialysis outcomes. Considering the central role of peritoneal dialysis (PD) in home dialysis, an important and readily estimable measure is the duration of PD before initiation of hemodialysis. We estimated the cumulative incidence of attrition due to initiation of hemodialysis among patients who recently initiated PD in the United States and assessed variability of incidence among age strata.

Methods: We analyzed United States Renal Data System Standard Analysis Files. We identified all patients who initiated PD in the home setting between January 1, 2011, and September 30, 2018, and within one year after diagnosis of end stage kidney disease (ESKD). We classified patients into cohorts of age 18-44, 45-64, 65-74, and ≥75 years. Overall and within age strata, we estimated the 5-year cumulative incidence of conversion to hemodialysis, with accounting for the competing risks of death and kidney transplantation.

Results: The cohort included 111,464 patients who initiated PD. The cumulative incidence of conversion to hemodialysis was 22.4% at 1 year, 33.9% at 2 years, 41.4% at 3 years, 46.3% at 4 years, and 49.4% at 5 years (figure). During those 5 years, 25.4% of patients died while receiving PD and 12.8% received a kidney transplant, thereby resulting in only 12.4% of patients still performing PD after 5 years. Among patients aged 18-44 years, 1-year (5-year) cumulative incidence of conversion to hemodialysis was 23.3% (51.1%); corresponding estimates were 22.3% (52.0%) among patients aged 45-64 years (48.3%), 21.9% among patients aged 65-74 years, and 22.5% (41.6%) among patients aged ≥75 years.

Conclusions: Regardless of age, between 22% and 23% of patients who initiated PD during the first year of ESKD transferred to hemodialysis within one year. Patient training is a critical component of the peritoneal dialysis (PD) program to ensure safe dialysis outcomes. However, there is a lack of clarity on how long patients should be trained before initiating PD at home. In this analysis, we evaluate the associations between the length of PD training and patient outcomes (early treatment attrition, peritonitis, and hospitalizations) among patients prescribed automated PD (APD).

PO0969

Length of Peritoneal Dialysis Training and Risk of Early Treatment Attrition

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Background: Patient training is a critical component of the peritoneal dialysis (PD) program to ensure safe dialysis outcomes. However, there is a lack of clarity on how long patients should be trained before initiating PD at home. In this analysis, we evaluate the associations between the length of PD training and patient outcomes (early treatment attrition, peritonitis, and hospitalizations) among patients prescribed automated PD (APD).

Methods: Adult patients who initiated APD between 2017-2019 and received PD training at Fresenius Kidney Care facilities within 30 days of home treatments were included. Crude and case-mix adjusted risk of early PD attrition (discontinuation from PD within 3 months of enrollment due to switch to HD, death, or loss to follow-up) were compared between patients with a shorter (≤5 days), medium (6 to 10 days), and longer (>10 days) lengths of training. Early rates of peritonitis and hospitalizations were compared between patients with ≤10 days vs >10 days of training.

Results: 11,039 patients who received training ≤30 days prior to APD initiation were included. Compared to patients with a shorter PD training (n=3,333), patients with a medium length of training (n=6,310) had no significant difference in the risk of early attrition (Figure 1). Patients with longer PD training (n=1,396) had a lower risk of early attrition when compared to shorter PD training patients in the crude analysis, and no significant difference when controlled for case-mix variables (significant confounders: vintage, residual kidney function, and body surface area). There were no differences in the early rates of peritonitis and all-cause and peritonitis-related hospitalizations between patients receiving training for >10 days vs ≤10 days.

Conclusions: There were no significant associations between length of PD training and risk of early treatment attrition, hospitalizations, or peritonitis among automated PD patients.

Funding: Commercial Support - Fresenius Medical Care North America

Figure 1

PO0970

Identifying Patients on Peritoneal Dialysis at High Risk of Transfer to Hemodialysis Using a Modified Surprise Question

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Background: Transfer from peritoneal dialysis (PD) to hemodialysis (HD) is associated with poor outcomes. Available prediction models of modality transfer are limited to the incident PD population. Simple predictive tools are needed to help guide risk stratification and subsequent clinical interventions to avoid unwanted modality transfer. We report on the correlates of nurse prediction of high risk using the question “Would you be surprised if this patient transfers to HD in the next 6 months?” (PD Surprise Question [PDSQ]).

Methods: This observational study included 1362 adults on PD receiving care at 35 centers in 3 states in the US, managed by a non-profit dialysis organization. A ‘no’ response to the PDSQ indicated high risk. Using multivariable logistic regression with backward elimination, we evaluated characteristics associated with being identified as high risk, including socio-demographic variables, BMI, primary kidney disease, vintage, comorbid conditions, renal and dialysate clearances, serum albumin, sodium, phosphorus, potassium, nPNA, last 3 months peritonitis and hospitalization, and insurance type. We used multiple imputations to handle missing data.

Results: Responses were obtained from 95/112 (85%) nurses for 1193/1362 (88%) patients. Mean age was 59 (SD: 16) years, 41% were female, median ESRD vintage 37 (IQR: 11 – 44) months and 46% had diabetes. 198 (17%) patients were identified as high risk. In the final model, patients were more likely to be identified as high risk if they were hospitalized in the last 3 months (odds ratio [OR]: 1.52, 95% confidence interval [CI] 1.30-1.74, p<0.0002). Having a higher serum sodium (for 1 meq/L: OR: 0.95, 95% CI 0.90-1.00, p=0.032), being married (OR: 0.76 95%CI 0.52-1.00, p=0.029), and longer PD vintage (for 1 month: OR: 0.99, 95%CI 0.98-1.00, p=0.013) were associated with lower odds of being identified as high risk.

Conclusions: The PD surprise question is a simple tool to assess the risk of transfer from PD to HD. Identified correlates of risk are consistent with high risk factors from the literature for transfer to HD. We are currently observing outcomes of included patients to examine the performance of the PDSQ to predict transfer to HD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

328
Machine Learning-Driven Prediction of Peritoneal Dialysis Technique Failure

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Background: Despite increased focus on starting and keeping dialysis patients on home therapy, Peritoneal Dialysis (PD) and Home Hemodialysis (HHHD) rates are lower than desired. Two areas of opportunity are 1) keeping PD patients healthy so they can remain on PD longer and 2) transitioning PD patients to HHHD when appropriate. To identify patients at risk of leaving PD in the short-(1-3 month) and long-term (3-6 month) timeframes, two machine learning (ML) models were developed. Along with risk scores, these models identify the factors driving increased risk to aid in prolonging time on PD while also allowing adequate notice to prepare for permanent access placement and HHHD education.

Methods: Data were extracted for PD patients (n=53022) from 2016-2019; patients contributed one set of observations for each month they were on PD (n=823892 patient months). PD failure was defined as the first discharge from PD lasting over 30 days, and was coded as ‘1’ if the patient changed modality in the next 1-3 or 3-6 months for the short- and long-term models, respectively. All other observations were coded as ‘0’, including censored events such as transplantation, loss to follow-up, or death. Two XGBoost ML models were trained using 80% of the dataset, with 20% used for evaluating model performance using 237 variables, derived from laboratory measurements, infection and hospitalization history, and other relevant clinical parameters.

Results: Evaluation of model performance on withheld data showed an area under the curve of 0.75 and 0.67 for the short- and long-term models, respectively. Patients were classified as High, Medium, or Low risk for each of their short- and long-term predictions. In the short-term model, the risk category dropped in the next 3-6 months for patients at high risk, a rate almost 5 times higher than average and 12 times higher than low risk patients. For long-term predictions, 14% of high risk patients dropped in the next 3-6 months, 6% of medium risk, and 2% of low risk.

Conclusions: The two ML models showed good discrimination between patient risk categories for both short- and long-term timeframes. Further work is underway to gauge the clinical utility of these tools, these tools offer the potential to improve care of “failing” PD patients, reduce morbidity of transitions, and increase optimal starts with dialysis access.

Funding: Support - Fresenius Medical Care

Nurse-Based Educational Interventions in Patients with Peritoneal Dialysis: A Systematic Review and Meta-Analysis

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Background: Peritoneal dialysis (PD) is a major renal replacement therapy modality for patients with end-stage renal disease (ESRD) worldwide. As poor patient self-care could lead to serious complications, including peritonitis, exit-site infection, technique failure, and death, several nurse-based educational interventions have been introduced. However, these interventions have varied and been supported by small-scale studies so the effectiveness of nurse-based educational interventions on clinical outcomes of PD patients have been inconclusive.

Methods: We performed a systematic search using PubMed, Embase, and CENTRAL. Selection criteria included Randomized Controlled Trials (RCTs) relevant to nurse-based education interventions in ESRD patients with PD in the English language up to February 20, 2020. The meta-analyses were conducted using a random-effects model to evaluate the summary outcomes of peritonitis, PD-related infection, mortality, transfer to hemodialysis, and quality of life (QOL).

Results: Of 7,240 potential studies, 61 theme-related abstracts were selected for further full-text articles screening against eligibility criteria. Ten studies (1,404 PD patients in seven countries) were included in the systematic review. Eight studies (1,363 PD patients in five countries) were included in the meta-analysis. Sleep QOL in the intervention group was significantly higher than control (mean difference 12.76, 95% CI 5.26–20.27). There was no difference between intervention and control groups on peritonitis, PD-related infection, transfer to hemodialysis, and overall QOL.

Conclusions: The two ML models showed good discrimination between patient risk categories for both short- and long-term timeframes. While further work is underway to gauge the clinical utility of these tools, these tools offer the potential to improve care of “failing” PD patients, reduce morbidity of transitions, and increase optimal starts with dialysis access.

Funding: Support - Fresenius Medical Care

Technique Failure in the Dominican Republic National Peritoneal Dialysis Program

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Background: Technique failure is a critical concern in peritoneal dialysis (PD), and it’s associated with significant risk of patient lost. Technique failure is defined as transferral to HD 30 days after initiation of therapy or death within 30 days of transfer to HD.

Methods: This is a retrospective multicenter observational cohort study of incident Peritoneal Dialysis patients conducted between January 1st 2016 to December 31st 2020. Competing risk events were death and kidney transplantation, and patients were censored for recovery of kidney function, withdrawal or suspension of the therapy, and loss of a caregiver. Disease characteristics and baseline demographics were included. Data are expressed as mean ± standard deviation for continuous variables and as frequency counts and percentages for categorical variables. Incidence rates were performed for transfer to HD and finally, logistic regression analysis between the inferential type variables to determine the risk between having a history of diabetes mellitus and the variables of death and transfer to HD were calculated using an Odds Ratio analysis with 95% confidence intervals for comparing the 3 risk levels.

Results: A total of 2326 patients were included, 59% men; the mean age was 57 ± 16 years, 53% had a diagnosis of Diabetes Mellitus (DM) and 65% had a basic educational level. 151 patients were censored (11%). Risk events were 1096 of which death accounts for 108 (7%) and PD Peritonitis 13% and ultrafiltration failure 13%.

Conclusions: The technique failure rate is similar to the reported in RTS Colombian PD Program, but below the mean of Latin American countries reports. Still, improvement needs to be done in the catheter implant technique and mortality rates.

PD Peritonitis

Quality of Life (Sleep)
Conclusions: In this single center observational study, peritoneal catheters placed laparoscopically with careful abdominal rectus tunneling allowed for larger volume dialysis exchanges without concern for supine positioning or intermittent use. One leak was noted and no other complications for an acceptable leak rate of 4% in this small study. This study demonstrates that PD can be initiated sooner post dialysis and larger volumes are well tolerated.

PO0975
Converting ESKD Patients on Peritoneal Dialysis to Hemodialysis Post Cardiac Surgery: A Necessity or Comfort
Elisa Basili,1 Milad Matta,2 Aimen Liaqat,1 Adam Fawaz,1 Georges Nakhoul,2 Joanna J. Taliercio,2,1 Juan C. Calle,2,1 Serge C. Harb,1 Haytham Elgharably,1 Susana Arrigain,1 Jesse D. Schold,1 Remy Daou,1 Ali Mehdi,2,1 Cleveland Clinic, Cleveland, OH; 2Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH; 1Université Saint-Joseph, Beirut, Lebanon.

Background: End-stage kidney disease (ESKD) patients on peritoneal dialysis (PD) undergoing cardiac surgery are sometimes converted to hemodialysis (HD) post-surgery. The reasons for this conversion are not well defined in the literature. We sought to examine the reasons cited for converting PD patients to HD post operatively after undergoing major cardiac surgery.

Methods: We examined ESKD patients on PD undergoing cardiac surgery from 2009-2019 using an electronic health records (EHR)-based Cardio-Thoracic Surgery (CTS) registry at the Cleveland Clinic. We identified PD patients who were converted to HD postoperatively. We reviewed the EHR to identify the main causes for conversion.

Results: 62 ESKD patients on PD undergoing major cardiac surgery were identified. 16 patients, representing more than a quarter, were converted to HD post operatively. Out of those converted, 31.25% were converted for absolute indications (18.75% for PD catheter malfunction, 3.125% for gait abnormalities), 25% for gait abnormalities, 25% for concern of pericardio-peritoneal communication. 67.5% were converted for less clear and relative indications (25% based on clinician preference, 47.5% for hemodynamic instability or requiring vasopressors). Results are displayed in (Table 1).

Conclusions: A small percentage of PD patients are converted to HD for absolute indications. Most patients are converted based on relative indications including lack of familiarity with PD and hemodynamic instability. As the number of ESKD patients on PD is expected to increase, a better understanding of the outcomes of PD patients post cardiac surgery is needed. In addition, more education is urgently needed to increase the comfort of practitioners managing PD patients in special situations that might be amenable to prescription alterations without premature transition to hemodialysis.

Table 1

PO0976
Effect of Low-Dose PD in Elder Population on Protein Energy Wasting, Functionality, and Quality of Life
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Background: Elder population currently involves 55% of those who initiate dialysis. Age-associated pathologies, functional status (FS), protein energy wasting (PEW) and quality of life (Qol) need to be considered. CAPD can cause PEW, loss of functionality and QoL decline, adjusting treatment to Intermittent Ambulatory PD (IAPD) (low-dose) has the intention to decrease disadvantages while maintaining the benefits. The aim of this study was to evaluate the effect of low-dose PD on PEW, functionality and Qol.

Methods: A retrospective cohort of patients 60 years and older was analyzed. IAPD was defined as less than 16hrs of treatment per day. Clinical, biochemical data were collected. Katz, Lawton-Brody scales and EQ-5D-5L questionnaire were applied.

Results: 90 patients were on IAPD. Prescription of hrs/day of dialysis did not correlate with residual ureas (r =-0.52, p=0.612). Questionnaires: QoL, EQ-5D-5L found the majority of patients were in the highest/positive scores for every category assessed. In the same way, 44% of the patients had 80 points or more in their perception of Qol. (fig.1). FS was found to be associated with albumin and phosphorus (r=0.306, p=0.015; r =0.312, p=0.027). Functionality, 67% of patients were classified as independent (figure 2) and FS was associated with albumin, uretras and VAS QoL. (r =0.462, p=0.000; r =0.416, p=0.000; r =0.407, p=0.000 respectively). A model to identify the predictors of functionality was made. It was found that female, age >75y, ureass<500m/d, albumin >3.5g/dl and hours of dialysis predict negatively scores. The interaction between hours of dialysis and age have the biggest effect size.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO0977
A Uremic Pig Model for Peritoneal Dialysis Research
Jooet C. de Vries,1 Maaike K. van Gelder,1 Anneke S. Munninkhof,1 Sabbir Ahmed,2 Diënty Hazenbrink,1 Tri Q. Nguyen,1 Koen Vaessen,2 Jaap A. Joles,1 Marianne C. Verhaar,1 Karin G. Gerritsen,1 1University Medical Center Utrecht, Utrecht, Netherlands; 2Utrecht University, Utrecht, Netherlands.

Background: The renewed interest in home dialysis requires a translational uremic large animal model to evaluate innovations in peritoneal dialysis. Ideally, toxin plasma levels should be comparable to those in dialysis patients, without requiring maintenance dialysis for survival. To this end, we developed a pig model with stable moderate chronic kidney disease.

Methods: CKD was induced in five female pigs by bilateral subtotal renal artery embolization aiming for embolization of ~85-90% of total kidney tissue. Temporary aggravation of uremia was induced with gentamicin (10 mg/kg twice daily for 7 days). We hypothesized this approach would lead to stable CKD without the need for maintenance dialysis. Peritoneal transport was assessed with a standard peritoneal permeability assessment.

Results: After embolization, urea and creatinine levels increased from 1.6±0.2 to 7.5±1.0 mM and 103±12 to 338±60 µM, respectively, followed by stabilization within 2 weeks to 2.5±1.0 mM and 174±25 µM, respectively. GFR (iohexol clearance) decreased from 49 mL/min to 28 mL/min. Gentamicin induced temporary acute-on-chronic kidney injury with peak urea and creatinine concentrations of 17.0±6.1 mM and 932±504 µM, respectively (Figure 1), while potassium (range 4.1-4.7 mM) and phosphate (range 2.33±2.67 mM) remained stable. Peak indoxyl sulfate and hippuric acid levels were 10.5 ± 0.85 mg/L and 75.3 ± 81.5 mg/L, respectively. Peritoneal dialysis, although complicated by peritonitis, could be successfully applied. Peritoneal transport assessment showed a low transport status (D/P creatinine (4h): 0.45±0.12) with an MTAC of 9.6±3.0, 4.6±2.5, 3.4±2.2 mL/min for urea, creatinine, and phosphate respectively.

Conclusions: We have established a pig model with stable moderate CKD without the need for maintenance dialysis. Temporary-on-demand acute-on-chronic kidney injury, resulting in uremic solute levels representative for ESKD, allows evaluation of novel dialysis methods.

Figure 1. Urea (left) and creatinine (right) plasma levels after administration of gentamicin (day 0). Mean ± SD, n=10 administrations in n=5 pigs.

PO0978
Recurrent Abdominal Pain in a Patient on Peritoneal Dialysis
Sandipan Shringi, Sri Vibhavari Guntupalli, Kristin M. Corapi. Saint Vincent Hospital, Worcester, MA.

Introduction: Abdominal pain can have many differentials in patients on peritoneal dialysis (PD). Some of them, including fungal peritonitis, requires PD catheter removal and a change in dialysis modalities. Here we present a case of recurrent abdominal pain in a patient on peritoneal dialysis which highlights the importance of prompt diagnosis.
Case Description: 40-year-old female with end stage renal disease secondary to systemic hyperoxaluria (SH) presented for 3 year clinic appointment after her system was disconnected with leakage of PD fluid. PD effluent revealed white count of 300 with 2% neutrophils. She was treated empirically for peritonitis. 11 days later her fungal culture grew Candida famata and she was admitted with intermittent abdominal pain associated with nausea and weakness. She was hemodynamically stable, and her exam was significant for epigastric tenderness with normal looking PD catheter site. Her white count was elevated to 13,000 with unremarkable metabolic panel. CT abdomen was unremarkable. A repeat PD effluent had white count of 40. Her PD catheter was removed the next day and she was switched to hemodialysis. She was treated with 10 days of oral fluconazole. On review, she had been having intermittent abdominal pain with PD effluent sometimes showing high white count for which she got multiple antibiotic courses for either presumed or culture positive bacterial peritonitis. She had also grown positive fungal culture about 18 months ago with Candida albicans and Streptococcus viridans which went unnoticed.

Discussion: Fungal peritonitis can be catastrophic for patients on PD. Treatment involves prompt catheter removal and systemic antifungal treatment. Given its dire consequences, prevention is paramount. The ISPD recommends using anti-fungal prophylaxis when PD patients receive antibiotic courses. Risk factors include previous bacterial peritonitis and antibiotic use. This case demonstrates the need to follow cultures as fungal growth is slow and can take weeks. It is important to have a high index of suspicion for a fungal organism when cultures are negative. This patient received antibiotics on several occasions but only developed fungal peritonitis on 2 occasions which raises concern on antifungal prophylaxis. Further studies are indicated to determine number needed to treat to decide on need for antifungal prophylaxis.

PO0979
Micrococcus Peritonitis Complicating Peritoneal Dialysis
Martin L. Li,1 Ankur Shah,2,3 ‘Brown University Warren Alpert Medical School, Providence, RI; 2Rheode Island Hospital, Providence, RI.

Introduction: Peritonitis is one of the most common and consequential complications of peritoneal dialysis. Micrococcus sp are catalase-positive, coagulase-negative, gram-positive cocci that are increasingly recognized as opportunistic pathogens in patients with immunocompromised hosts or indwelling catheters. These bacteria have been rarely implicated as causative in peritonitis. We present a case of peritonitis due to Micrococcus sp and review the pertinent literature.

Case Description: A 55-year-old female with history of ESKD due to diabetic kidney disease, CAD s/p CABG, and hypertension presented with a 1 day history of cloudy effluent. She had no prior peritonitis episodes. Vital signs were stable and exam was notable for a soft non-tender abdomen and clean and dry exit site without discharge or granulation tissue. Effluent was hazy in appearance. Administration of empiric vancomycin and gentamicin was initiated, varying in duration of 24 to 48 hours. Effluent leukocyte count was 204 cells/µL with 58% neutrophils. Intraperitoneal vancomycin was continued for 3 weeks due to intermittent low troughs. Further history revealed intermittent mask use while performing exchanges. After completion of treatment, with complete resolution of symptoms and peritoneal cell count. Cell count and culture were repeated 1 month later during evaluation of abdominal pain eventually found to be due to constipation. Leukocyte count was 6 cells/µL but culture again grew Micrococcus sp. After culture was repeated once more and remained peritonitis negative, repeat treatment to eradicate was attempted with 2 more weeks IP vancomycin but culture remained positive. Eventually the catheter was removed due to a change in living situation. After 5 months of hemodialysis, peritoneal catheter was replaced and the patient was restarted on peritoneal dialysis, after which time she has not had a peritonitis episode.

Discussion: We present the 10th case of Micrococcus sp. Peritonitis in a peritoneal dialysis patient. Prior cases have been associated with breaks in technique and have shown a pattern of recurrence with resultant technique failure being very common. Attempted treatments have included vancomycin, cefazolin, cefazidime, and ticlopin. In the prior 9 published cases, 4 resulted in technique failure. This case and review of the pertinent literature. For dialysis patient. Prior cases have been associated with breaks in technique and have

PO0981
Chylous Peritoneal Fluid in a Patient on Peritoneal Dialysis Taking Nifedipine
Lauren E. Macaree, Dena E. Rifkin, Tyler Woodell, O. Alison Potok. University of California San Diego, La Jolla, CA.

Introduction: Chylous fluid in peritoneal dialysis (PD) patients may appear with lymphatic system disruption. This can be due to lymphatic obstruction, exudation through vessels, or via a lymphopertitoneal fistula.

Case Description: A 78-year-old man with ESKD due to diabetic nephropathy, transitioned five weeks prior from HD to PD, presented with newly cloudy PD fluid. His past medical history included hypertension, coronary artery disease, and monoclonal gammopathy of undetermined significance. He reported a newly cloudy white initial drain with lower abdominal pain, but denied fever, vomiting or diarrhea. He denied a breast in sterile technique. Medications included hydralazine, cinacalcet, furosemide, nifedipine, omeprazole, calcium acetate and darbepeotin. He was hemodynamically stable and had no abdominal tenderness. Laboratory results revealed a leukocytosis of 11.7 × 10^9/L. Peritoneal fluid was milky (figure 1a) with 101 white blood cells (4% neutrophils); gram stain and culture were negative. Triglycerides were 96 and 62 mg/dL in the PD fluid and serum, respectively. Etiologic work-up was negative for malignancy, pancreatitis, cirrhosis, trauma and tuberculosis. Chylous nature of the PD fluid resolved within a day of nifedipine discontinuation (figure 1b). The patient self-resumed nifedipine weeks later and the milky fluid recurrring the following day again before reinitiating after its repeat cessation.

Discussion: This patient had the onset of chylous PD fluid 5 weeks after initiating PD, which resolved with cessation and recurrence with reinstatement of his long-term nifedipine. The mechanism of calcium channel blockers (CCB) – related chylous ascites is not well established. Some have suggested it may be related to the lipophilic nature of CCB. Patients on PD with higher peritoneal membrane transport may be at higher risk. Genetic factors may predispose to this phenomenon. Nephrologists should be aware of this rare complication of CCB use in PD patients. More research is needed to better understand the underlying pathophysiology of this rare condition.
PO0982
Severe Bleeding and Deep Inferior Epigastric Pseudoaneurysm After PD Catheter Removal
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Introduction: In this case, the removal of a PD catheter with deep cuff calcification results in pseudoaneurysm formation with hemorrhage and hospitalization.

Case Description: A 56-year-old woman with end-stage kidney disease was switched from PD to HD due to worsening uremia and PD catheter removal was organized. At the time of catheter removal heavy calcification around the deep Dacron cuff was seen. Catheter removal should be done in settings equipped with interventional radiology support in the event of complication. We report a case of a 56 year old woman with end stage kidney disease previously on peritoneal dialysis (PD) with subsequent live donor kidney transplant on immunosuppression, who presented with right lower quadrant abdominal cellulitis and deep abscess around the catheter site. Post transplant, her PD catheter was removed, however, the catheter site never healed completely. Although she did have multiple superficial skin infections in the past, those resolved with antibiotics. But this specific cellulitis, did not improve despite multiple antibiotic regimens, and further imaging studies revealed she had developed an abscess. The abscess was managed by surgical incision and drainage with debridement of the skin, subcutaneous tissue, fascia, and muscles around the whole catheter tract. Aeromonas hydrophila was found as the causative organism.

Discussion: This is an important learning case in PD catheter removal and highlights the following: - Poorly controlled bone mineral disease may lead to excessive calcification of the deep Dacron cuff and DIEP vessels. - When heavy calcification of the PD cuff is seen, catheter removal should be done in settings equipped with interventional catheter removal.

Calcium-phosphate balance while on PD

<table>
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<th>Month</th>
<th>Calcium (mg/dL)</th>
<th>Phosphorus (mg/dL)</th>
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<td>2.10</td>
<td>200</td>
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<td>2.00</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

332

PO0983
A Case of Abdominal Wall Abscess Caused by Aeromonas hydrophila in Prior Peritoneal Catheter Site in an Immunocompromised Patient Post Kidney Transplant
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Introduction: Aeromonas hydrophila is a gram-negative rod-shaped bacterium found in aquatic ecosystems; it has been identified as the causative organism of different opportunistic infections in the immunocompromised and there is growing evidence of infection in the immunocompetent. This pathogen has been implicated in acute gastroenteritis, soft tissue infections, meningitis, peritonitis and sepsis among others.

Case Description: We report a case of a 56-year-old woman with end-stage kidney disease previously on peritoneal dialysis (PD) with subsequent live donor kidney transplant on immunosuppression, who presented with right lower quadrant abdominal cellulitis and deep abscess around the catheter site. Post transplant, her PD catheter was removed; however, the catheter site never healed completely. Although she did have multiple superficial skin infections in the past, those resolved with antibiotics. But this specific cellulitis, did not improve despite multiple antibiotic regimens, and further imaging studies revealed she had developed an abscess. The abscess was managed by surgical incision and drainage with debridement of the skin, subcutaneous tissue, fascia, and muscles around the whole catheter tract. Aeromonas hydrophila was found as the causative organism.

Discussion: To our knowledge, this is the first case of an A. hydrophila abscess associated with peritoneal dialysis catheter. Firm association between aeromonads and the use of intravenous indwelling devices has already been demonstrated. We hypothesize that her deep seeded infection could be associated with the intrinsic ability of A. hydrophila to form biofilms upon detecting a suitable surface, making them more virulent. The formation of biofilm has been associated with exponential growth as the source of pathogenicity of this bacteria in pisciculture studies. This characteristic could be one of the factors contributing to reported cases of peritonitis and intravenous hemodialysis catheters by A. hydrophila. Further elucidation of A. hydrophila virulence factors in humans can provide insight on prevention of PD catheter associated infections by A. hydrophila.

PO0984
Mesenchymal Stem Cell Exosomes Protect Mouse Peritoneal Injury Induced by Human Peritonitis Dialysis Effluent
Fang Yu,1 Kehong Chen, Jia Chen, Yani He. Army Military Medical University, Daping Hospital, Department of Nephrology, Chongqing, China.

Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies for it. The purpose of this study was to investigate the protective effect of exosomes secreted by mouse bone marrow mesenchymal stem cells (MSC) on peritoneal injury and to reveal the mechanism.

Methods: Forty-two male C57BL/6 mice were randomly divided into six groups: a control group (2.5% glucose dialysate), a peritonitis-effluent group (The overnight 2.5% glucose dialysate of patients with peritonitis), a high glucose (4.25%) dialysate group, a peritonitis-dialysate+exosome group, a high glucose dialysate+exosome group, and a control group (2.5% glucose dialysate). The mouse model of peritoneal injury was constructed by intraperitoneal injection of human peritonitis dialysis effluent continuously for 42 days. The mice in the exosome treatment group received intraperitoneal injection of MSC-exosomes twice. The level of peritoneal structural and functional damage was detected. The effect of MSC-exosomes was validated in vitro.

Results: Peritoneal transport and structure was significantly impaired in the peritonitis-effluent group and the high glucose dialysate group after 42 days, and was significantly higher than control group. The results suggested that human peritonitis dialysis effluent could be used to construct a mouse model of peritoneal injury. Masson staining showed that fibrosis degree of exosome treatment group was significantly less than peritonitis-effluent group. Immunohistochemical analysis showed that expressions of mesothelial markers E-cadherin and ZO-1, neutrophil granulocytes (MPO) and macrophages (F4/80), and fibrosis markers (collagen I, a-SMA) in exosome treatment group were significantly lower than peritonitis-effluent group. Peritoneal ultrafiltration function of exosome treatment group was significantly improved compared to peritonitis-effluent group. In vitro experiments showed that exosomes could down-regulate the secretion of IL-1β, IL-6 and TGF-β1 by peritoneal mesothelial cells stimulated by high glucose dialysate, maintain expression of mesothelial cell marker (E-cadherin), and inhibit mesenchymal marker (a-SMA), suggesting that exosomes could inhibit the transdifferentiation of peritoneal mesenchymal cells (MMT).

Conclusions: MSC-exosomes can alleviate peritoneal fibrosis by inhibiting peritoneal mesothelial cell-mesenchymal cell transdifferentiation.
**PO0985**

**Dual Therapy with JAK1/2 Inhibitor and Losartan Attenuates Dialysate-Induced Angiogenesis in Polycystic Rats**

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**Background:** Long term peritoneal dialysis (PD) is limited by reduced efficacy over time. Early peritoneal membrane (PM) injury is characterized by inflammation which progresses to hyperviscosity and fibrosis. JAK-STAT signaling mediates inflammatory pathways, including angiogenesis signaling. Our previous study showed dual therapy with JAK1/2 inhibitor (JAK1/2i) and an ARB maintains PM structure and function in rats with polycystic kidneys (PKC) chronically infused with 4.25% Dianease x 16 wks. By using VEGF2R as an endothelial marker, we further investigated if this dual therapy can attenuate chronic dialysate infusion induced hyperviscosity in this rat model.

**Methods:** PCK rats were used. Dialysate infusions were performed BID via an implanted subcutaneous port in the neck tunneled to the intraperitoneal cavity. The following treatments were administered: (1) No surgery/infusions; (2) 4.25% Dianease; (3) 4.25% Dianease + JAK1/2i (5mg/kg BID); (4) 4.25% Dianease + Losartan (5mg/kg BID); and (5) 4.25% Dianease + Losartan + JAK1/2i (5mg/kg BID each). Parietal peritoneum was used for immunohistochemical staining of VEGF2R, which was digitally quantified by using Qu Path program. Data were analyzed by one-way-ANOVA followed by Tukey test. Results are mean ± SEM.

**Results:** VEGF2R staining was significantly elevated after 16 weeks IP infusion of 4.25% Dianease alone. JAK1/2i significantly reduced VEGF2R expression; losarant tended to reduce VEGF2R, but this did not reach significance. Dual therapy with JAK1/2i and losartan resulted in the greatest reduction of VEGF2R

**Conclusions:** Long-term JAK1/2i, or JAK1/2i plus losartan intraperitoneal treatment reduces angiogenesis. Angiogenesis inhibition is advocated to maintain residual renal function, by adding JAK1/2i, the combination also protects peritoneal structure/function by reducing angiogenesis.

**PO0986**

**The Effect of Far-Infrared Therapy on the Peritoneal Expression of Glucose Degradation Products in Diabetic Patients on Peritoneal Dialysis**

Chih-Ching Lin, Chih-Yuan Niu. Taipei Veterans General Hospital, Taipei, Taiwan.

**Background:** Peritoneal dialysis (PD) is a treatment modality for end-stage renal disease (ESRD) patients. Dextrose is a common osmotic agent used in PD solutions and its absorption may exacerbate diabetes mellitus. PD solutions also contain glucose degradation products (GDPs) that may lead to encapsulating peritoneal sclerosis (EPS). A previous study showed that far-infrared (FIR) therapy improved a patient’s gastrointestinal symptoms due to EPS. Due to limited literature, this study aims to investigate dialysate GDPs and peritoneal function in diabetic patients on PD.

**Methods:** A prospective analysis conducted in a single center. The participants were recruited from the peritoneal dialysis outpatient department from November 25, 2016 to September 5, 2018. We included the patients who met the following criteria: (1) ESRD patients aged 20-90 years without receiving FIR therapy within 12 months; (2) receiving continuous ambulatory peritoneal dialysis or automated peritoneal dialysis; (3) no history of peritonitis, cerebrovascular accident, myocardial infarction, or receiving any cardiovascular intervention in the past 3 months. Patients were allocated to two groups based on their underlying DM history. Both groups of PD patients received FIR therapy for 6 months. We collected the last daily bag of peritoneal dialysate and calculated the dialysate concentration of GDPs and clinical data in PD patients pre- and post-FIR therapy.

**Results:** Thirty-one PD patients were enrolled and underwent 40 min of FIR therapy twice daily for six months. We demonstrated the effect of FIR therapy on the following: (1) decrease of methylglyoxal (p = 0.02), furfural (p = 0.005), and 5-hydroxymethylfurfural (p = 0.03), (2) increase of D/D0 glucose ratio (p = 0.03), and (3) decrease of potassium levels (p = 0.008) in both DM and non-DM patients, as well as (4) maintenance and increase of peritoneal K+ in DM and non-DM patients, respectively (p = 0.03). FIR therapy is a non-invasive intervention that can decrease dialysate GDPs in PD patients by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

**Conclusions:** In conclusion, our study demonstrated that FIR therapy can decrease PD patients’dialysate GDPs by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

**PO0987**

**Cumulative Dialysate Glucose Exposure Is a Risk Factor for Peritoneal Sclerosis in Pediatric Peritoneal Dialysis Patients Using Neutral-pH Fluids**

Yoko Shirai,1 Kenichiro Miura,1 Taro Ando,1 Atsutoshi Shiratori,1 Naoto Kaneko,1 Kiyonobu Ishizuka,1 Sekiko Taneda,2 Daishi Hirano,1 Yoichiro Yamaguchi,1 Kazuhiro Honda,1 Motoishi Hatori,3 Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan; 2Department of Pathology, Tokyo Women’s Medical University, Tokyo, Japan; 3Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan; 4Yamaguchi Pathology Laboratory, Chiba, Japan; 5Department of Anatomy, Showa University School of Medicine, Tokyo, Japan.

**Background:** The benefits of neutral-pH fluids for preventing peritoneal dialysis (PD)-related peritoneal sclerosis have been established, however, advanced peritoneal sclerosis still has been described in pediatric PD patients using neutral-pH fluids (Kidney Int 2018). The factors associated with peritoneal pathological changes after long-term use of neutral-pH fluids have not been elucidated.

**Methods:** Pediatric PD patients using only conventional acidic fluids (conventional group) and those using only neutral-pH fluids (neutral-pH group, n=33) for more than one year were analyzed. Propensity score matching was performed to compare the peritoneal pathological changes between groups. Clinical risk factors including PD duration and cumulative dialysate glucose exposure for peritoneal pathological changes in the neutral-pH group were analyzed using generalized linear model. Furthermore, immunofluorescence studies were performed on vascular endothelial growth factor (VEGF-α), cytokertatin, and α-smooth muscle actin (α-SMA); a myofibroblastic marker of epithelial-mesenchymal transition (EMT).

**Results:** Age at biopsy was 1.3 (1-6) years (median [IQR]) and duration of dialysis was 3.2 (1.7-5.3) years. The neutral-pH group showed less peritoneal deterioration except for higher submesothelial microvesSEL density (P = 0.01) than conventional group. In the neutral-pH group, the cumulative dialysate glucose exposure was an independent risk factor for increased thickness of the submesothelial compact zone [OR, 1.004; 95%CI, 1.001-1.007] and submesothelial microvesSEL density [OR, 1.003; 95%CI, 1.000-1.005].

**Conclusions:** Cumulative dialysate glucose exposure correlated with the proportion of VEGF-α-positive areas (P<0.01, r=0.55). In immunofluorescence study, VEGF-α (+) cells comprised cytokertatin (+) cells and α-SMA (+) cells.

**PO0988**

**Predicting Patient and Technique Survival in a Cohort of Incident Peritoneal Dialysis (PD) Patients According to Peritoneal Small Solutes Transport Rate (PSTR)**

Rafael A. Gomez,1 Abdul Rashid T. Qureshi,2 Joanna Stachowska-Pietka,3 Malgorzata Debowska,4 Jacek Waniewski,5 Bengt Lindholm,2 Baxter Renal Care Services, Cali, Colombia; 2Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; 3Nalecz Institute of Biocybernetics and Biomedical Engineering Polish Academy of Sciences, Warsaw, Poland.

**Background:** The association between PSTR and clinical outcomes in patients undergoing chronic peritoneal dialysis (PD) is uncertain. We explored the association between PSTR with mortality and technique survival in a large cohort of incident patients undergoing PD in Colombia.

**Methods:** In a cross-sectional study, 8170 PD patients, treated with APD (2705, 33.1%) and with CAPD (5465, 66.9%), who underwent peritoneal equilibration test to determine dialysate/plasma glucose ratio (G/D) 4 hours were classified into low (16.0%), slow average (35.4%), fast average (32.9%) and fast (15.7%) PSTR categories. Demographic, clinical and laboratory variables were evaluated. During median follow-up of two years, 2633 (32.2%) patients died, 1079 (13.2%) patients transferred to hemodialysis, and 661 (8.1%) patients underwent renal transplantation. All-cause and cardiovascular disease (CVD) mortality risk and technique survival were analyzed with competing-risk regression with transplantation as competing risk.

**Results:** Patients with fast as compared to slow PSTR were older, more often male or diabetic (DM), and had lower Hb and serum albumin levels. In competing risk analysis, after adjusting for age, sex, body mass index, residual kidney function, presence of diabetes and hypertension and circulating albumin, Hb, and phosphate levels, higher PSTR associated with greater risk (subdistribution hazard ratio, sHR) for all-cause mortality (fast average: sHR 1.13, 95%CI 1.00-1.26; p=0.04) and fast: sHR 1.19, 95% CI 1.04-1.36; p=0.01), and CVD-related mortality (fast average: sHR 1.18, 95% CI 0.99-1.41; p=0.05) and fast: sHR 1.19, 95% CI 0.97-1.46; p=0.08), and reduced technique survival (fast average: sHR 1.15, 95% CI 0.95-1.38; p=0.13) and fast: sHR 1.24, 95% CI 1.02-1.52; p=0.05).

**Conclusions:** These results suggest that fast and fast average PSTR associates with increased mortality risk and tendency towards reduced technique survival when analyzed using adjusted competing-risk regression models.

**Funding:** Commercial Support - Baxter Renal Care Services; Baxter Healthcare Corporation.
PO0989

Multifrequency Bioimpedance Is a Useful Adjunct to Control Fluid Overload in PD Patients
Szu-Yuan Li, Chiao-Lin Chuang, Jinn-Yang Chen. Taipei Veterans General Hospital PD team Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Fluid overload is a well recognized phenomenon in many peritoneal dialysis (PD) patients, but a balance between reduction of dry weight and preservation of residual renal function (RRF) is mandatory. We hypothesize that, to achieve an ideal dry weight, adjustment by multifrequency bioimpedance (MF-BIA) guide offers less adverse effect on residual renal function than that by clinical judgment alone.

Methods: The hydration status of various body compartments were measured using a MF-BIA device (Inbody 720, Biospace). The normalized hydration score was defined as extracellular water (ECW)/total body water (TBW). All patients were evaluated monthly for 6 months. The dry weight of study group was adjusted according to MF-BIA to avoid dehydration, and the dry weight of control group was determined clinically. Ambulatory blood pressure, anti-hypertension medication dosage, serum biochemical parameters, and RRF were recorded monthly. IL-6 and hs-CRP will be checked before and after the study.

Results: 93 stable PD patients (48 in study and 45 in control group) completed the study. ECW/TBW ratio was higher in PD patients than sex- and age-matched healthy subjects. (Figure 1). In PD patients, the ratio of ECW/TBW was positive correlated to age (r = 0.334), peritoneal D/P ratio (r = 0.518), systolic BP (r = 0.520) and negative correlated to urine volume (r = -0.526), serum albumin (r = -0.658). After 6 months intervention, study group decreased 1.2 kg and control group gained 0.2 kg. The study group had a better systolic and diastolic BP control and a higher serum albumin (3.75 ± 0.61 vs 3.48 ± 0.68 g/dl, p = 0.047). The RRF has no difference between two groups.

Conclusions: Our results showed that correction of fluid overload would improve blood pressure control. Being an objective tool to assess hydration status of various body compartments, MF-BIA is a useful adjunct to correct fluid overload without the loss of RRF in our short-term study.

PO0990

Associations Between Loop Diuretic Use and Outcomes Among Patients Treated with Peritoneal Dialysis
Jiacong Lu1, Dena E. Cohen,1 Carey Colson,1 Steven M. Brunelli,1 Francesca Tentori,1 Martin J. Schreiber,2 Davita Clinical Research, Minneapolis, MN; 3Davita Inc, Denver, CO.

Background: Among hemodialysis patients, an active loop diuretic prescription at the time of dialysis initiation is associated with a lower hospitalization rate and other favorable outcomes, compared to no prescription. Whether this finding extends to patients initiating peritoneal dialysis (PD) is not known.

Methods: Data used for this retrospective study comprised electronic health records and US Renal Data System claims data merged through direct linkage. Included patients initiated PD at a large dialysis organization between 01 Jan 2006 and 30 June 2014, were nonoliguric at dialysis start (24-hour urine collection >200 cc), and had Medicare insurance. Exposure was determined on the basis of an active, filled supply for a loop diuretic spanning day 90 of PD. Outcomes were considered from day 91 of PD through the first of death, loss to follow-up, or study end (31 Dec 2014) and were compared across exposure groups using appropriate statistical models adjusted for imbalanced patient characteristics.

Results: Among patients initiating PD with a loop diuretic prescription (N=792), the hospitalization rate during follow-up was 1.77 admissions/patient-year (pt-yr), compared to 1.75/pt-year for those without (N=1363), corresponding to an adjusted incidence rate ratio (aIRR) of 1.05 (95% confidence interval [CI] 0.97-1.15). Mortality was likewise comparable between groups, with crude rates of 0.21 and 0.18 deaths/pt-year, respectively (aIRR 1.05, 95% CI 0.82-1.35). No substantial differences were observed between exposure groups with respect to serum potassium, renal Kt/V, or time to transition to hemodialysis.

Conclusions: Among patients initiating PD, no beneficial associations were observed between loop diuretic use and any of the outcomes examined.
Identifying Peritoneal Dialysis (PD)-Associated Peritonitis Using Medicare Claims

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Background: Medicare fee-for-service (FFS) claims offer a population-based approach to PD-associated peritonitis that may offer valuable insights into predictors, trends and preferred practices.

Methods: We used United States Renal Data System (USRDS) standard analysis files for claims (inpatient, outpatient and physician-supplier), eligibility, modality and demographic information. The sample consisted of PD patient-months from 2013 through 2017 characterized by Medicare FFS coverage and paid claims for dialysis or hospital services. We identified ICD-9 and ICD-10 diagnosis codes for peritonitis, including those that do not clearly distinguish peritonitis from catheter infections/inflammation (“catheter codes”). A new peritonitis episode was defined as a peritonitis claim >30 days from any prior peritonitis claim or >30 days from the initial peritonitis claim for a prior episode.

Results: The sample included 88,396 adult patients (128,000 observed patient-years), yielding 510,000 peritonitis claims and 75,000 peritonitis episodes. Coding was heterogeneous with no single diagnosis code present on the majority of claims. Peritonitis episodes were inferred from aggregated claims (mean 6.3, median 2). Half of episodes were exclusively outpatient, 7% exclusively inpatient, and 16% exclusively comprised of catheter code claims. The overall peritonitis rate was 0.59 and 0.49 episodes per patient-year with and without inclusion of catheter codes respectively. Peritonitis rates declined 4%/year from 2013-2017, and varied by age, race (Black > White > Asian), and ESKD vintage.

Conclusions: Coding heterogeneity indicates a lack of standardization and need for clearer coding guidance. We found differences between races, ages, and patient vintages, and declining rates from 2013-2017. These rates are 2-fold higher than reported in US-PDOPPS by Perl et al (AJKD 2020) which is not restricted to Medicare. Claims are an important data source for peritonitis, but more work is needed to validate these rates.

Funding: Other NIH Support - Agency for Healthcare Research and Quality.

Protective Association Found Between Peritoneal Dialysis Patients Prescribed Home Antibiotics Kits and In-Center Hemodialysis Transition

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Background: Peritonitis is a complication of peritoneal dialysis (PD) and is likely associated with technique failure. To decrease time to peritonitis treatment, Fresenius Kidney Care (FKC) clinicians can prescribe broad-spectrum intraperitoneal and oral antibiotic kits. Kits are self-administered by home PD patients for suspected wet contamination or peritonitis per algorithm. The study purpose is to assess hemodialysis (HD) transition as well as peritonitis among PD patients receiving a home antibiotic kit.

Methods: This retrospective cohort study identified FKC PD patients prescribed home antibiotic kits between June 1, 2019 and June 30, 2020. Home FKC PD patients not receiving kit during same period composed the control pool. Patients are matched in a 1:4 ratio on clinical and demographic data using propensity scores. Patients were followed up to 6 months for transition to HD and first peritonitis event. Outcomes were analyzed with weighted competing risk Cox Proportional Hazards Models.

Results: 2,888 treatment and 10,613 controls were studied. Of the 2,888 treatment patients and weighted 1,921.2 matched controls, 11.9% and 13.5% transitioned to HD, respectively. A 0.88 hazard ratio (p=0.0448) determined treatment group is 12% less likely to transition to HD at any point during follow-up period. 10.4% treatment patients and 8.5% controls have at least one peritonitis event. The treatment group is 23% more likely to have a Peritonitis event (p=0.0019).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Critical care nurses prepped for patient autotransfusion

J Am Soc Nephrol 32: 2021 Peritoneal Dialysis Poster

Conclusions: The study identified a protective association in HD attrition for home PD patients receiving peritoneal kits vs. positive association between patients receiving the kits and peritonitis. These findings may reflect residual confounding factors such as clinicians prescribing kits for patients at higher risk of peritonitis for uncontrolled or unmeasurable factors since kits do not prevent peritonitis but increase uniformity of treatment. The findings justify need for further research including prospective randomized studies.

Funding: Commercial Support - Fresenius Medical Care

PO995
Assessing Physician Clinic Practices and Competencies in Performing Peritoneal Dialysis Catheter Flushing During the 10-Day Global Period

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Background: Early flushing of peritoneal dialysis (PD) catheters theoretically reduces the incidence of catheter obstruction by decreasing formation of fibrin strands or blood clots. Early flushing also enables timely identification of catheter dysfunction, creating an opportunity to revise the catheter prior to scheduled training and initiation of therapy. It is unknown how frequently PD access providers perform flushes in their clinics, but Centers for Medicare & Medicaid Services (CMS) has indicated that services performed within 10 days following catheter placement (global period) are the responsibility of PD access providers. Therefore, under existing regulations, dialysis organizations generally defer to access providers to perform catheter flushes during this global period. The purpose of this study is to access current practices of PD access provider clinics (surgeon, interventional nephrologist or radiologist) in performing catheter flushes.

Methods: PD access providers placing catheters for a large dialysis organization in the southwestern United States during 2020 were surveyed. The 3-question survey asked: 1) PD access provider specialty, 2) if the clinic performed catheter flushes, and 3) the background of the staff person assisting the physician with clinic procedures. Responses were acquired by direct or telephone contact with the physician or clinic staff.

Results: Survey responses were obtained for all 201 providers who placed PD catheters during 2020 (Table). Significantly, none of the PD access provider clinics elected to provide these services during the global period for patient safety and optimal patient outcomes.

Funding: Commercial Support - DaVita, Inc.

PO996
Peritoneal Dialysis Catheter Flushing Leading to Syncope from Vagal Nerve Stimulation

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Introduction: Peritoneal dialysis is the most common form of home dialysis. Complications can arise however any time the peritoneum is invaded such as during surgery. The patient is a 57-year-old male on PD secondary to developing progressive IgA nephropathy. The patient suffered from an inguinal hernia which required open repair surgery. The patient is a 37-year-old male on PD secondary to developing progressive IgA nephropathy. The patient subsequently developed hypotension, diaphoresis and near syncope. This process continued every time the patient’s peritoneal catheter was flushed. 500 mL’s of 2.5% warm saline was used to fill the patient resulting in the same near syncopal episode. With repositioning of the patient’s catheter the symptoms completely resolved.

PO997
Pharmacokinetics of Intraperitoneal Vancomycin in Patients on Automated Peritoneal Dialysis

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Background: It is unclear if the pharmacokinetics of vancomycin is the same during automated peritoneal dialysis (APD) where cycle exchanges may affect the systemic, peritoneal, and urinary disposition of drug.

Methods: This was a prospective pharmacokinetic study in peritonitis-negative patients on APD. A single dose of vancomycin (20 mg/kg) was administered through the peritoneum and allowed to dwell for at least 15 hours. Patients underwent four drug-free exchanges following the initial dwell period. Plasma, dialysate and urine were collected over the course of 7 days for pharmacokinetic analysis. A non-comparitional analysis was used to estimate vancomycin pharmacokinetic parameters.

Results: Four patients enrolled and completed the study with no adverse events. Three patients had residual renal function. Following a median (range) dwell of 14.6 (14.2 – 17.6 hours), the mean ± SD observed maximum plasma concentration was 28.7 ± 4.9 mg/L with a mean ± SD bioavailability of 98.5 ± 1.4% prior to starting the cycler. The overall mean plasma clearance estimated from study start to completion was 7.3 ± 1.2 mL/min. In patients with residual renal function, the mean ± SD vancomycin renal clearance was 3.1 ± 1.5 mL/min.

Conclusions: Despite the small sample size, this pilot study suggest that the dwell time has important implications for systemic vancomycin exposure, time to therapeutic plasma concentration, and dosing. Dose is driven by dwell time while the cycler determines the dosing interval. Rapid exchanges from APD will determine the frequency of dosing rather than the adequacy of absorption when vancomycin is given in the peritoneum.

Funding: Other NIH Support - Edwin Lam was supported by an NIH T32 training grant (GM008562) at the time of study conduct.

Plasma, dialysate, and urine pharmacokinetic parameters following a single intraperitoneal dose.

1 Represents the total plasma clearance for the duration of the study.
2 Represents the total plasma clearance during the dialytic exchange period.
3 Median value reported.
4 Min and Max range reported.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Effect of Velphoro on Serum Phosphate and Albumin in Peritoneal Dialysis Patients

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Background: Hyperphosphatemia is common in patients on peritoneal dialysis (PD). Restricting phosphorus in the diet often leads to a decrease in protein intake, which may result in hypoalbuminemia. Hypoalbuminemia is associated with an increased risk of morbidity and mortality in PD patients. In observational studies, saccharin oxyhydroxide (SO), an iron-based phosphate binder, was associated with improved phosphate control and higher serum albumin in hemodialysis patients. Whether SO improves phosphate control and nutritional status in PD patients is unknown.

Methods: We performed a prospective, open-label, 6-month, pilot study of 17 adult PD patients from the Denver Metro Area. Patients had to use automated peritoneal dialysis for at least 3 months, have a serum albumin ≥ 3.8 g/dL, and have serum phosphate ≥ 5.5 mg/dL or ≥5.5 mg/dL on a binder other than SO. Patients currently on phosphate binders underwent a 2-week washout period. Participants were started on SO at a dose of 1 tablet daily with meals. Serum phosphate was checked monthly and the dose of SO was titrated to a goal serum phosphate of < 5.5 mg/dL. The primary outcome was change in serum phosphate and serum albumin over 6 months.

Results: The mean (SD) age and dialysis vintage was 55 ± 13 years and 3.8 ± 2.7 years, respectively. The majority of patients were male (65%), white (82%), and non-Hispanic (64.7%). 88% of patients were on a phosphate binder at baseline and the majority were on sevelamer (73%). Twelve patients completed the study. Two patients withdrew due to side effects (diarrhea), 1 patient changed to hemodialysis and 2 patients died (unrelated to the study). Mild diarrhea and change in stool color were the most frequently reported side effects. Results are shown in Table 1. Serum phosphate decreased significantly from baseline but there was no significant change in serum albumin. Phosphate binder pill burden significantly decreased.

Conclusions: Serum phosphate decreased significantly with fewer phosphate binder pills/day after switching to SO. There was no change in serum albumin.

Funding: Commercial Support - Fresenius Renal Therapies

Prognostic Significance of Plasma Vaspin and Adiponectin Levels in Peritoneal Dialysis Patients

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Background: Adiponectin and vaspin are key adipokines that play important roles in the physiology of adipose tissue and contribute to the pathogenesis of metabolic disturbances in chronic kidney disease (CKD). We explored the prognostic role of plasma adiponectin and vaspin levels in peritoneal dialysis (PD) patients – a population that may be at high risk of cardiovascular and renal events due to metabolic syndrome, obesity, and cachexia are common.

Methods: We measured plasma adiponectin and vaspin levels in a cohort of new PD patients and analyzed their relation with patient survival.

Results: We studied 152 patients. Their mean age was 58.38 ± 11.67 years; 102 (67.1%) were men, 92 (60.5%) were diabetic. The median plasma adiponectin level was 67.1% were men, 92 (60.5%) were diabetic. The median plasma adiponectin level was 31.98 ng/ml (Interquartile range [IQR]: 16.81-49.49 mg/ml; median vaspin level 0.18 (IQR: 0.01-0.32) ng/ml. There was no significant correlation between plasma adiponectin and vaspin levels. Plasma adiponectin level had modest correlations with Charlson’s comorbidity score (r = 0.174, p = 0.039), triceps skin fold (r = -0.269, p = 0.001), and vaspin levels. Plasma adiponectin level had modest correlations with Charlson’s comorbidity score (r = 0.174, p = 0.039), triceps skin fold (r = -0.269, p = 0.001), and vaspin levels. Plasma vaspin level correlated with carotid-to-femoral pulse wave velocity (r = -0.240, p = 0.005), triceps skin fold (r = 0.198, p = 0.018), and extracellular to Intracellular fluid volume ratio (r = -0.170, p = 0.047). After adjusting for clinical confounders, plasma adiponectin and vaspin levels were significantly predicted patient survival (adjusted hazard ratio [AHR] of adiponectin 1.018, 95% confidence interval [CI] 1.004-1.031, p = 0.010; AHR of vaspin 1.018, 95%CI 1.008-1.029, p=0.001).

Conclusions: Plasma adiponectin and vaspin levels were independent predictors of patient survival. Our results suggest that adiponectin and vaspin are involved in different pathways of metabolic disturbance in uremia.

The Impact of Peritoneal and Urine Protein Losses on Nutritional Status in Peritoneal Dialysis Patients


Background: The etiology of malnutrition in peritoneal dialysis (PD) patients is multifactorial, but the peritoneal protein losses (PLL) and proteinuria may be important contributing factors. We aimed to evaluate if the total protein losses (into urine and dialysate) in PD patients have an impact on their nutritional status.

Methods: A retrospective observational study of PD patients over the first year in PD. Demographic, clinical, and analytical data were collected at baseline (time of PD initiation), 6 and 12 months later. Nutritional status was assessed using normalized protein catabolic rate (nPCR), body mass index (BMI), lean body mass (LBMI), and body fat mass (BFM). The total amount of 24h urine and dialysate protein losses (ProtUrDial) and delta (Δ) values (difference between the end of follow-up period and baseline) of continuous variables were also calculated.

Results: Twenty patients were enrolled (55±8±10.8 years; 65% male). Except for serum albumin (sAlb), which changed significantly from the baseline to the end of the follow-up period (p=0.001), there were no differences in protein loss into dialysate (ProtDial), proteinuria (ProtUrine), nPCR, BMI, LBMI, and BFM over time. In the 3 time points there was a significant positive correlation between ProtUrine and nPCR (r=0.563, p=0.01; r=0.584, p=0.031; r=0.611, p=0.004, respectively). At the end of the follow-up period, we verified a negative correlation between sAlb and ProtUrDial (r = -0.512, p = 0.033). There was no correlation between ProtDial and nutritional parameters status, however, there was a positive correlation between ΔProtUrine and ΔBMI (r=0.492; p=0.028). Regarding ΔProtUrDial, we verified a negative correlation with ΔsAlb (r=-0.664; p=0.026) and, although not significant, a positive correlation with Δ%BFM (p=0.573; p=0.066).

Conclusions: The PLL has already been linked to malnutrition in PD patients. However, we found that the total amount of protein losses daily (into urine and dialysate), and not one each individually, seems to influence the nutritional status of PD patients. Besides, proteinuria appeared to have a greater impact on nutritional changes than peritoneal losses. However, more studies with larger samples are needed to clarify this association.

MMP-7 Affects Peritoneal Ultrafiltration Associated with Elevated Aquaporin-1 Expression via MAPK/ERK Pathway in Peritoneal Mesothelial Cells

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Background: Peritoneal membrane dysfunction and the resulting ultrafiltration failure are the major disadvantages of long-term peritoneal dialysis (PD). It becomes increasingly clear that mesothelial cells play a vital role in the pathophysiological changes of the peritoneal membrane. Matrix metalloproteinases (MMPs) function in the extracellular environment of cells and mediate extracellular matrix turnover during peritoneal membrane homeostasis. Aquaporin-1 (AQP-1), one of the water-specific channel proteins distributed in the endothelium lining the peritoneal capillaries, facilitates the osmotic transport of water across the capillary endothelium, thereby playing an essential role in ultrafiltration during PD.

Methods: Human peritoneal mesothelial cell (HPMCs)/line (HMrSV5) strain was continuously cultured in vitro and stimulated with MMP-7. Western Blot, RNA isolation, real-time PCR and immunofluorescence assay were used to detect the expression of MMP-7, AQP-1 and mitogen-activated protein kinases (MAPKs) phosphorylation in HMrSV5 cells, to verify that MMP-7 affects peritoneal ultrafiltration associated with elevated aquaporin-1 expression via MAPK/ERK pathway in peritoneal mesothelial cells.

Results: We showed that dialyse MMP-7 levels markedly increased in the patients with PD, and the elevated MMP-7 level was negatively associated with peritoneal ultrafiltration volume. Interestingly, MMP-7 could regulate the cell osmotic pressure and volume of human peritoneal mesothelial cells. Moreover, we provided the evidence that MMP-7 activated mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinases 1/2 (ERK) pathway and subsequently promoted the expression of aquaporin-1 (AQP-1) resulting in the change of cell osmotic pressure. Using a specific inhibitor of ERK pathway abrogated the MMP-7-mediated AQP-1 upregulation and cellular homeostasis.

Conclusions: In summary, all the findings indicate that MMP-7 could modulate the activity of peritoneal cavity during PD, and dialyse MMP-7 might be a noninvasive biomarker and an alternative therapeutic target for PD patients with ultrafiltration failure.

Funding: Clinical Revenue Support
PO1002
Psychosocial Impact of COVID-19 Pandemic on Patients with ESKD on Peritoneal Dialysis
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Background: The mortality rate from COVID-19 is remarkably high in elderly patients and those with chronic conditions. Increases in physical and mental stress among patients with chronic conditions, especially end-stage kidney disease, were expected to have occurred in response to the COVID-19 pandemic. This study reports that the psychosocial impact of the COVID-19 pandemic on patients receiving peritoneal dialysis.

Methods: During the pandemic, we surveyed the mental health of patients with end-stage kidney disease on peritoneal dialysis at a single center. Depression using with BDI score was evaluated and then compared in peritoneal dialysis patients between before and the pandemic declaration. We also surveyed patient satisfaction with the self-care services associated with peritoneal dialysis under the pandemic period.

Results: One-third of the survey respondents (n=176) were moderately to extremely worried about their physical health being impacted by the pandemic, while 20% moderately to extremely worried about their mental and emotional health being impacted. About half of participant reported feeling that they were unable to handle their personal problems and that things were out of their control. However, most felt that they could retain control over the important things and overcome their difficulties. Despite COVID-19 pandemic, no significant changes in depression scores were apparent between before and during the pandemic. Most participants were satisfied with the in-home self-care services delivered by either telephone or remote monitoring.

Conclusions: Many participants reported that they were afraid of COVID-19, but most patients with PD felt that they could overcome the crisis. The COVID-19 pandemic did not affect the depression of patients receiving peritoneal dialysis.

PO1003
Peritoneal-Mediastinal Communication Complication in Peritoneal Dialysis
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Introduction: Increased intra-abdominal pressure is a well-recognized non-infectious complication of peritoneal dialysis (PD) resulting from instillation of dialysate fluid into the peritoneal cavity. Peritoneal-pleural communication causing hydrothorax is well-described in the literature, but cases of peritoneal-mediastinal communication are scarce.

Case Description: A 36-year old Caucasian man with end-stage kidney disease secondary to calciuneurin inhibitor nephrotoxicity and BK virus nephropathy transitioned to continuous cyclic peritoneal dialysis (CCPD) after one year of intermittent hemodialysis (iHD). He presented to our institution nine months after starting CCPD primarily because of complications related to prior heart transplantation. He underwent cardiac surgery and did not have any problem with his CCPD in the immediate post-operative period and was discharged. One month later, however, he presented with increased serous drainage from his sternal incision site and reduced ultrafiltration. A chest CT scan revealed a partially loculated anterior chest wall subcutaneous fluid collection. He was taken to the operating room and was found to have a peritoneal-mediastinal communication. He was successfully managed with “low-pressure” PD by using reduced fill volumes for all his exchanges, which also allowed optimal healing of the muscle flap closing the communication. Transition to iHD was considered, but he had no vascular access options for all his exchanges, which also allowed optimal healing of his fill volumes. Unfortunately, one and a half months after his last hospitalization, he succumbed to septic shock secondary to trans-lumbar PICC-associated Candida glabrata fungemia.

Discussion: A peritoneal-mediastinal communication should be suspected in an otherwise asymptomatic patient on PD with reduced ultrafiltration who underwent any form of chest surgery. Clinical suspicion can be confirmed either through CT peritoneography or intraoperatively. Management with a trial of “low-pressure” PD is feasible and can be successful, particularly if iHD is not an option. A multi-disciplinary approach involving our surgical colleagues is also crucial to ensure appropriate patient care.

PO1004
Sweet Pleural Effusion in a Peritoneal Dialysis Patient
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Introduction: Pleural Effusions are frequently seen in dialysis patients with an incidence as high as 80%, with a variety of possible differential etiologies.

Case Description: A 62-year-old female with HHPEF, DM and ESRD due to biopsy proven diabetic nephropathy recently started on nightly continuous cyclic PD with a prescription of 4 exchanges of 2.5% Dextrose solution with 2 liters fill volumes with a dwell time of 1840 min for a total time of 8.5 hrs with no day dwells presented with dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining a dwell time of 1h40 min for a total time of 8.5 hrs with no day dwells presented with dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining dyspnea.

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338
tubes, thus its accumulation reflects an impaired RKF. Our study aimed to evaluate if serum levels of β2MG could be used as a complementary tool for evaluating RKF in peritoneal dialysis (PD) patients.

Methods: For this retrospective cohort study, we evaluated 423 urine samples of 166 patients who were in the PD program of Hospital das Clinicas, HC FMUSP, Universidade de Sao Paulo, Brazil. To be included, patients needed to have been followed for at least 90 days prior to PD initiation. Urine samples were collected at the end of a 24-hour period and immediately sent to the laboratory. We measured serum β2MG levels using a fluorescence polarization immunoassay (FP-I), which was performed on a cobas 8000 analyzer. The median time from PD initiation to the last sample was 1.5 years (IQR: 1.0, 2.0).

Results: We found a correlation between renal Kt/V and β2 microglobulin (r = -0.656, p < 0.0001), serum creatinine and urinary volume (r = -0.682, p < 0.0001), and serum creatinine (r = -0.603, p < 0.0001), and urinary volume (r = -0.682, p < 0.0001). ROC curve revealed that β2 microglobulin had a high performance to predict renal Kt/V, with a sensitivity of 70% and 81.7% according to the best cutoff. The specificity varied from 71.5% to 84.2% for Kt/V cutoff 0.5, 1.0, 1.5 and 2.0.

Discussion: Based on the good correlation found, on serum β2MG and urea renal Kt/V, we suggest that β2MG can be a useful tool to estimate the RKF. This findings can be particularly useful in patients who have difficulties in storing or collecting a 24-hour urine sample.

PO1008

Unusual Cause of Recurrent Shortness of Breath in a Peritoneal Dialysis Patient

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Introduction: Pleuroperitoneal leak (PPL) is an unusual cause of recurrent pleural effusion in patients on peritoneal dialysis (PD). It is a rare complication and occurs in less than 2% of cases. Diagnosis is challenging and requires high clinical suspicion and awareness of this life threatening complication. Pleural fluid to serum glucose ratio >30 mg/dl is highly specific for detecting leak of high glucose dialysate into pleural cavity, however this needs to be interpreted in relation with the last dialysis session.

Case Description: A 72-year-old-female with history of end stage renal disease due to biopsy proven focal segmental glomerular sclerosis thought to be secondary to obesity started on CCPD one-month prior presented with worsening shortness of breath of 1 week duration. Workup was unremarkable except for chest X-ray that showed right side pleural effusion. A non-contrast CT chest did not show a diaphragmatic defect. She continued to have worsening SOB prompting an emergent thoracentesis that drained 1.6 L transudate pleural fluid. Pleural fluid to serum glucose gradient was normal at 5 mg/dl but pleural fluid to serum glucose ratio was >1. However, last PD session was 2 days prior to thoracentesis, which could explain this lower ratio. Due to inconsiderable [NL] results, it was decided to instill 300 mL of saline in the chest and then do a sequential CT chest. It showed interval re-accumulation of high-density pleural effusion, suggesting trans-diaphragmatic communication. Cardiothoracic surgery was consulted for repair of diaphragmatic defect; however, patient opted for hemodialysis instead.

Discussion: It is important to maintain high clinical index of suspicion in PD patients presenting with hydrothorax. Although high pleural fluid to serum glucose gradient is specific for PPL, pleural to serum glucose ratio >1 is another index that should be considered in addition to post- gastrografin imaging or technetium 99 peritoneal scintigraphy, especially if the last dialysis session was not recent and could potentially alter the biochemical assay results as happened in our case. Most cases of PPL occur soon after PD initiation, common on right side. For those who wish to continue PD, surgical repair is often required while transitioning to HD temporarily or doing low volume recurrent PD. Some case series have noted the defect to close spontaneously after holding PD.

PO1009

The Association Between Lower Serum Potassium Level and Increased Cardiovascular Death Among Patients Undergoing Peritoneal Dialysis

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Background: In patients undergoing peritoneal dialysis (PD), lower serum potassium concentration has been related to low nutrition status and suggested as a risk factor for all-cause and cardiovascular mortality. However, the risk of lower serum potassium concentration for cardiovascular death in patients using renin-angiotensin system (RAS) inhibitors or β-blockers is not clear. This study investigated the relationship between lower serum potassium concentration and cardiovascular death among Japanese patients undergoing PD.

Methods: We retrospectively included the 549 patients from our previous multicenter cohort study (Fukuoka Peritoneal Dialysis Database Study). The participants who had undergone PD for at least 90 days were registered from 1 January 2006 to 31 December 2016 and followed until they were transferred to hemodialysis, received a kidney transplantation, died during PD, or were lost to follow-up, or until 31 December 2017. The patients were divided into three groups according to the baseline serum potassium concentration (T1 ≤ 4.0, 4.0 < T2 ≤ 4.5, T3 > 4.5 mEq/L). We estimated the relationship between serum potassium concentration and cardiovascular mortality using a Cox proportional hazards model.

Results: During the median observation period of 2.3 years, 111 patients died of any cause, and 38 died of cardiovascular. After multivariable adjustment in the Cox proportional hazard model, lower serum potassium concentration was shown to be an independent risk factor for cardiovascular death; (hazard ratio 95% confidence intervals) T2 and T1 vs. T3 were 2.21 (1.77-2.67) and 2.67 (1.01-7.07), respectively. Stratified-analysis according to the use of RAS inhibitors, β-blockers, or a combination of both drugs showed that this relation was not modified by the use of these drugs.

Conclusions: This study showed that lower serum potassium concentration was associated with increased cardiovascular mortality in PD patients. There was no difference in the risk of lower serum potassium concentration for cardiovascular death according to the use of the RAS inhibitors and/or β-blockers in PD patients.
PO1010

Higher Serum Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio Was Associated with Increased Mortality Among Incident Peritoneal Dialysis Patients

Hae Won Noh, Soojeon Jeon, Jeong-Hoon Lim, Hye-Yeon Jung, Ji-Young Choi, Sun-Hee Park, Chan-Duck Kim, Yong-Lim Kim, Jang-Hee Cho. Department of Internal Medicine, Kyungpook National University Hospital, Korea Kyungpook National University Hospital, Daegu, Republic of Korea.

Background: A few studies have shown that serum total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C) was a risk factor for cardiovascular mortality in the general population. This study was aimed to evaluate the association of TC/HDL-C with mortality in incident peritoneal dialysis patients.

Methods: We enrolled Total of 6,30 incident peritoneal dialysis patients from 2008 to 2015 in a multi-center, prospective cohort study of Korea. Participants were stratified into quintiles according to the baseline TC, HDL-C, or TC/HDL-C. The association between all-cause mortality and each lipid profile was evaluated using multivariate Cox regression analysis.

Results: During a median follow-up period of 70.3 ± 25.2 months, 185 deaths were recorded. The median TC/HDL-C was 4.54 ± 2.51. Highest TC/HDL-C group showed highest body mass index, percentage of diabetes, and serum albumin level. Multivariate analysis revealed that the highest quintile of the TC/HDL-C (>5.60) was associated with increased risk of all-cause mortality (hazard ratio 1.69, 95% confidence interval 1.04 to 2.76; P = 0.036), whereas neither of TC and HDL were associated with mortality. Increased serum TC/HDL-C was also independent risk factor for mortality in the patients with old age over 50 years, non-diabetes, and any cardiovascular disease.

Conclusions: The single lipid marker of TC or HDL-C could not predict mortality in PD patients. However, non-traditional lipid profile such as increased serum TC/HDL-C ratio was independently associated with an increased risk of all-cause mortality in PD patients.

PO1011

Peritoneal Dialysis Caregiver Scope and Functions: A Systematic Scoping Review

Tanawin Nopsoon,1,2 Chitsanucha Chumsri,1 Piyawat Kantagowit,1 Krit Pongpirul.3,5 Thailand PD Outcomes and Practice Patterns Study (PDOPPS) Steering Committee Chulalongkorn University Faculty of Medicine, Bangkok, Thailand; 4Harvard University T H Chan School of Public Health, Boston, MA; 1Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.

Background: Caregivers play important roles in peritoneal dialysis (PD) care. Classifying PD self-care tasks is important for determining the PD caregiver roles. As the scope and functions of PD caregiver in published literature have been inconsistent, we aimed to systematically explore the variations of the term caregiver in high-quality PD studies.

Methods: We performed a systematic search using PubMed, Embase, and CENTRAL for randomized controlled trials and observational studies relevant to a caregiver in ESRD PD studies. We aimed to systematically explore the variations of the term caregiver in high-quality PD studies.

Results: Of 2,514 potential studies relevant to a caregiver in ESRD patients with PD, 299 theme-related abstracts were selected for further full-text articles screening according to eligibility criteria, and 111 were included in the systematic review (72,101 patients in 34 countries). In terms of word choice, “caregiver(s)” was used in 86.4%, “caretaker(s)” in 20.7%, and other words were used in 13.5% of included studies. Only 8.1% of studies gave the explicit definitions of those words. The most referred person is the parents (40.5%), followed by a spouse (37.8%), other family members (37.8%), children (34.2%), non-relative non-healthcare workers (25.2%), friends (20.7%), and healthcare workers (19.8%). The explanation of functions for each word comprises 41.4%, with the PD-specific functions by 32.4%, instrumental activities of daily living by 9.9%, and basic activities of daily living by 5.4%.

Conclusions: PD caregiver has been broadly defined and vary across studies. PD-specific functions should be used for making the definition of PD caregiver clearer.
Methods: An end-vein to side-artery AVF was surgically created in the femoral vessels of rats which had previously been subjected to uremia via subtotal nephrectomy. At 1 and 2 weeks after AVF formation the arterial and venous limbs of the AVF were harvested for the assessment of gene and protein expression and the assay of SA-B-Gal activity. Femoral veins and arteries from rats subjected to sham surgery were used as controls.

Results: At 1 week after AVF creation mRNA levels of senescence drivers p16 and p21 were markedly elevated in AVF veins compared to sham veins, as were p21 protein levels; the AVF artery also displayed elevated p21 protein levels at this time point. At 2 weeks, p21 protein was again upregulated in both the vein and artery of the AVF, and protein levels of an upstream mediator in the p21 senescence pathway, p53, were significantly increased in the AVF artery; p53 levels did not achieve significance (p=0.083) in the AVF vein at this time point. Upregulation of SASP factors was also observed in the AVF artery at 1 week: mRNAs expression of PAI-1, IL-6, TNF-α and MCP-1 was robustly increased as compared to sham veins at 1 week after AVF creation. Additionally, miR21, which has been associated with vascular senescence, was markedly elevated in the AVF vein at 1 week post AVF placement. Finally, SA-B-Gal activity, an established marker of senescence was significantly increased in both the artery and vein compared to their sham counterparts at both 1 and 2 weeks post AVF surgery.

Conclusions: Using established criteria, this study demonstrates that the rat femoral AVF in the setting of CKD has a senescence phenotype similar to the murine AVF-CKD model. These findings thus demonstrate the development of senescence in another species subjected to an AVF in the presence of uremia.

Funding: NIDDK Support

PO1014

The Adaptive Response of the Vein to CKD: A Transcriptomics Perspective

Laisel Martinez,1 Akshara Sree Challa,1 Marwan Tabbara,1 Miguel G. Rojas,1 Juan C. Duque,1 Loay H. Salman,1 Roberto I. Vazquez-Padron,2,3 University of Miami School of Medicine, Miami, FL;1 Albany Medical College, Albany, NY;1 VA Miami Healthcare System, Miami, FL.

Background: The impact of CKD on gene expression in the vascular wall remains unknown, particularly in veins, despite their fundamental role as conduits for hemodynamic stress.

Methods: In this study, we investigated the CKD fingerprint on the transcriptome of basilic veins by analyzing 48 pre-access veins from end-stage renal disease patients and 20 veins from non-CKD trauma donors by bulk RNA sequencing.

Results: We uncovered 16,893 differentially expressed genes (DEG) between CKD and control individuals (log(FoldChange)>1, FDR<0.05). The presence of kidney disease caused a noticeable decrease in transcriptional activity in veins, with the downregulation of >97% of DEG transcripts. These included 6,081 non-coding RNAs, 3,826 protein-coding genes, and other miscellaneous transcripts. In contrast, a unique set of 462 genes was upregulated in CKD veins vs. controls, 161 of which corresponded to non-coding RNAs, 201 to protein-coding genes, and the rest to minor RNA biotypes. Gene set enrichment analysis (GSEA) identified a suppression of pathways related to vascular maintenance, cell morphogenesis, cell metabolism, and microtubule-based cytoskeletal functions. Interestingly, the protein-coding genes upregulated in CKD veins belonged to processes related to gas transport and detoxification of oxidative stress byproducts.

Conclusions: In conclusion, we have uncovered a profound suppressive effect of CKD on the venous transcriptome, likely affecting basic cell functions such as metabolism, cell division, and migration. We also identified a transcriptional signature of upregulated genes in response to oxidative stress which may play a fundamental role in cell survival in the CKD environment.

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

PO1015

Gender-Specific Risk Genes in Arteriovenous Fistula Failure

Roberto I. Vazquez-Padron,1 Marwan Tabbara,1 Miguel G. Rojas,1 Akshara Sree Challa,1 Juan C. Duque,1 Loay H. Salman,1 Laisel Martinez,1 University of Miami School of Medicine, Miami, FL;1 VA Miami Healthcare System, Miami, FL.

Background: Gender is known to play a role in arteriovenous fistula remodeling and risk of failure. However, the clinical and molecular mechanisms behind this phenomenon have not been elucidated.

Methods: To address this question, 48 pre-access veins obtained at the time of two-stage AVF creation (24 matured and 24 failed postoperatively) and 40 postoperative transposition samples (20 matured and 20 failed) were randomly selected from the University of Miami Vascular Biorepository and submitted for bulk RNA sequencing. Females and males were equally represented in both outcome groups and were similar in demographics and baseline characteristics. We searched for common and sex-specific differentially expressed genes (DEG) in pre-access veins and postoperative samples in association with failure.

Results: In the pre-access vein, we found 28 DEG between veins that matured or failed postoperatively (log(FoldChange)>1, FDR<0.05) and in common between both sexes. In the veins, 115 DEG were differentially expressed between both outcomes, whereas no female-specific DEG were detected in the same number of individuals. Principal component analyses demonstrated more transcriptional variability in both outcome groups in females, decreasing our power to identify female-specific genes in the female cohort. In postoperative samples, we found 156 DEG between fistulas that matured or failed and in common between both sexes. In addition, 143 female-specific and 153 male-specific genes were differentially expressed between outcomes, indicating gender relevant processes of postoperative remodeling. Both sexes showed a downregulation of genes related to responses to external stimuli and stress. However, gene set enrichment analysis (GSEA) revealed a suppression of cell-surface receptor signaling and cell adhesion mechanisms in males but not in females, suggesting a sex-specific effect in cell migration.

Conclusions: In conclusions, these analyses uncover potential differences in postoperative remodeling between females and males in relation to AVF failure. They also indicate a more complex transcriptional landscape in female tissues which may affect our ability to predict remodeling in this group of patients. These data may open the door to personalized medicine in preventing or treating vascular access complications.

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

PO1016

Inhibition of Phosphodiesterase Type 5A Prevents Pathological Cardiac Remodeling Following Arteriovenous Fistula Creation

Maheshika S. Somarathna,1 Taylor G. Lewis,2 Kevin A. Ingle,1 Tatyana Isayeva Waldrop,1 Jimmy C. Lee,1 'The University of Alabama at Birmingham, Birmingham, AL;2 Rosalind Franklin University of Medicine and Science Chicago Medical School, North Chicago, IL.

Background: Cardiac events are the most common etiology of mortality in hemodialysis patients. The gold standard of vascular access, the arteriovenous fistula (AVF), may adversely affect cardiac structural and functional remodeling leading to heart failure. We hypothesize that inhibition of cGMP catalysis with a selective phosphodiesterase type 5A (PDE5A) inhibitor, sildenafil, may induce more favorable cardiac remodeling following AVF creation.

Methods: Sildenafil was administered to 12-16 weeks old Sprague-Dawley rats two weeks prior to AVF creation and continued until sacrifice at 28 days. Cardiac structural and functional changes were evaluated by 1) 2D-echocardiography 2) measurement of collagen volume and oxidative stress and 3) evaluation of cardiac contractility.

Results: Sildenafil treatment significantly improves the pathological collagen degradation, reduces HNE expression, reverses desmin demineralization and focal mitochondrial clustering following AVF creation, as compared to the control. We also observed a significant increase in cardiac output and stroke volume without reversing LV dilatation which may suggest improvement in cardiac contractility.

Conclusions: PDE5A inhibition may provide a new treatment strategy for pathological cardiac remodeling following AVF creation.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1017
Pre-Access Vein Transcriptomics as a Predictor of Arteriovenous Fistula Failure: A Machine Learning Approach
Miguel G. Rojas,1 Laisel Martinez,1 Akshara Sree Challa,1 Marwan Tabbara,1 Juan C. Duque,2 Loay H. Salman,3 Roberto I. Vazquez-Padron,1,4 1University of Miami School of Medicine, Miami, FL; 2Albany Medical College, Albany, NY; 3VA Miami Healthcare System, Miami, FL.

Background: As the number of patients with end-stage renal disease continues to rise, the creation of a robust and efficient hemodialysis access is more important than ever. A mature arteriovenous fistula (AVF) is the preferred method for long-term hemodialysis. However, the nationwide maturation rate continues to be as low as 50-60%, and we currently lack an effective risk stratifying method to identify patients at higher risk of AVF failure.

Methods: To address this clinical need we developed a predictive model based on supervised machine learning from transcriptomics of the pre-access vein. Forty-eight pre-access veins obtained at the time of AVF creation (24 matured and 24 failed postoperatively) were randomly selected from the University of Miami Vascular Biorepository and submitted for bulk RNA sequencing. Both outcome groups were matched by age, sex, demographics, and baseline clinical characteristics. The highest expressing genes (normalized gene expression counts >200) were used as input in KNN, SVM, XGBoost, and other machine learning algorithms. Area under the curve (AUC) and receiver-operating characteristic (ROC) plots were used to compare the performance of the models relative to each other. The best performing algorithm, XGBoost, was optimized with the following hyperparameters [gamma=0.25, learning_rate=0.001, max_depth=4, reg_lambda=10, scale_pos_weight=3]. The SHapley Additive exPlanations (SHAP) analysis was then used to evaluate the highest contributing features to the XGBoost model.

Results: Ten highly predictive and abundantly expressed genes were identified using this methodology (RICK1, CLIC3, DNLAL1, FOXO4, TIMMDC1, GALNT11, CDH13, KLHC10, ZNF8, and DBT). Using these transcripts, the AUC in the logistic regression model is 97.6%.

Conclusions: In conclusion, this study has identified 10 potential pre-access gene predictors of postoperative AVF failure, which could be used clinically as a stratifying or risk management tool in vascular access patients.

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

PO1019
Arteriovenous Fistula Non-Maturation: Does the Immune System Play a Role?
Crystal A. Farrington,1 Gary R. Cutter,2 Michael Allon,3 1The University of Alabama at Birmingham Department of Medicine, Birmingham, AL; 2The University of Alabama at Birmingham School of Public Health, Birmingham, AL.

Background: Arteriovenous fistula (AVF) non-maturation is a persistent problem, particularly among female and Black patients. The immune system promotes several well-studied. We evaluated the association of serum panel reactive antibodies (PRA), a measure of immune system reactivity assessed in patients undergoing kidney transplant, with the following hyperparameters {gamma=0.25, learning_rate=0.001, max_depth=4, reg_lambda=10, scale_pos_weight=3}. The SHapley Additive exPlanations (SHAP) analysis was then used to evaluate the highest contributing features to the XGBoost model.

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

Table 1. AOR of 7 key variables for AVF non-maturation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>1.09</td>
<td>0.96 to 1.16</td>
<td>0.14</td>
</tr>
<tr>
<td>Race, Black</td>
<td>1.20</td>
<td>0.92 to 1.57</td>
<td>0.18</td>
</tr>
<tr>
<td>Race, Other</td>
<td>1.07</td>
<td>0.85 to 1.34</td>
<td>0.64</td>
</tr>
<tr>
<td>Race, Asian</td>
<td>1.05</td>
<td>0.83 to 1.32</td>
<td>0.64</td>
</tr>
<tr>
<td>Race, White</td>
<td>1.00</td>
<td>0.97 to 1.24</td>
<td>0.95</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>1.01</td>
<td>0.98 to 1.24</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>1.00</td>
<td>0.97 to 1.24</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Figure 1. ROC curves.
**PO1021**

The Association of Transition-to-Dialysis Planning and Healthcare Resource Use and Mortality in Patients with ESRD

**Insyba B. Poonawalla,**1 Kanchan Barve,1 Meghan C. Cockrell,2 Amal Agarwal,2 Adrienne W. Casebeer,3 Yong Li,1 *Humana Healthcare Research, Inc., Louisville, KY; 2Humana Inc, Louisville, KY.*

**Background:** The onset of ESRD is associated with poor outcomes and high mortality, and the role of transition-to-dialysis planning is not well understood. We evaluated the association between dialysis transition planning factors such as nephrologist care, vascular access placement, and place of index dialysis, with inpatient (IP) stays, emergency department (ED) visits, and mortality.

**Methods:** This retrospective study used the Humana Research Database to identify 7,026 patients, 19-89 years of age, diagnosed with ESRD between 1/1/17 and 12/31/17, enrolled in a Medicare Advantage Prescription Drug plan, with ≥12 months of continuous enrollment pre- and post-index date (i.e., first evidence of ESRD). Patients with a kidney transplant indication, hospice election, or dialysis pre-index were excluded. Transition-to-dialysis planning was defined as optimal, partial, or unplanned (Table 1). IP stays, ED visits, and mortality were evaluated within 12 months post-index.

**Results:** The cohort was 41% female, 66% White, with an average age of 70 years. An optimally planned, partially planned, and unplanned transition to dialysis occurred for 15%, 34%, and 44% of the ESRD cohort, respectively. Among patients with pre-index CKD stages 3a and 3b, 64%, and 55%, respectively, had an unplanned dialysis transition. For patients with pre-index CKD stages 4 and 5, 68% and 84%, respectively, experienced planning prior to dialysis initiation. In adjusted models, patients with partially or optimally planned transition to dialysis were 57% to 72% less likely to die, 20% to 37% less likely to experience an IP stay, and 80% to 100% more likely to experience an ED visit than patients with an unplanned transition. Higher ED utilization with planned transition was attributed to longer time to mortality, allowing more time for healthcare utilization.

**Conclusions:** A planned transition to dialysis was associated with improved outcomes and lower mortality. Targeting care coordination for patients with CKD stages 3a/3b may help slow disease progression and ensure a planned, safer transition to dialysis.

**Table 1. Transition-to-Dialysis Planning Definitions**

<table>
<thead>
<tr>
<th>Planning Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>All planning factors were accounted for by nephrologist before start of HD</td>
</tr>
<tr>
<td>Partial</td>
<td>At least one of the planning factors was accounted for by nephrologist</td>
</tr>
<tr>
<td>Unplanned</td>
<td>None of the planning factors were accounted for by nephrologist</td>
</tr>
</tbody>
</table>

**PO1022**

Prediction of Stenosis in Arteriovenous Fistula Using Video Image Analysis

Fanfan Zhu,1 Lin-Chun Wang,1 Alhaji Cherifi,2 Ohmmar Thwin,1 Lela Tisdale,1 Xia Tao,1 Paulo Paneque Galuzio,1 Norbert Shatynberg,2 Dean C. Predicid,2 Peter Kotanko,1,3 Renal Research Institute, New York, NY; Azura Vascular Care, New York, NY; 1Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** We developed a video image processing (VIP) technique with frequency domain analysis to predict stenosis in AVF. The study aimed to evaluate whether the degree of stenosis can be assessed using parameters from frequency domain signal analysis.

**Methods:** We employed VIP in 100 hemodialysis patients (age 63.3 ±14.1 years, 47 females) prior to endovascular arterio-venous fistula (AVF) interventions. A 1-minute video of the AVF area was recorded using a smartphone (Fig 1). We constructed time series based on pixel changes between two consecutive video frames (Fig 2-A) and used Fast Fourier Transform (FFT) to transform the time domain signals into the frequency domain (Fig 2-B). Parameters in the frequency domain included maximal (Max) and minimum (Min) amplitude, and frequency (F_min and F_max). AF was defined as F_max - F_min M2 was calculated by the squared ratio of the Max-to-median magnitude. The degree of AVF stenosis (%ST) was determined by angiography, the access flow (AF) by thermodilution.

**Results:** Data from 98 patients were analyzed. %ST was categorized into three groups: 60% stenosis (n=8), 70-80% (n=76), and 90% (n=14). AF correlated with %ST. Max, F_max, and AF were associated with %ST (Table 1). An algorithm was developed to predict degree of %ST based on patient characteristics and parameters of frequency domain analysis. In the respective three %ST groups the sensitivities to detect AVF stenoses were 88%, 86% and 100%, and the specificities 99%, 82% and 98% (Table 1).

**Conclusions:** VIP applied to videos taken with a smartphone may provide a contact-free method to estimate the degree of AVF stenosis. Validation studies in independent cohorts are needed to further assess the diagnostic capability of the proposed method.
Catheter-Related Bloodstream Infection Incidence and Associated Mortality Risk: Analysis of Merged USRDS-Medicare Claims

Aaron Kenneth 

Mortality Risk: Analysis of Merged USRDS-Medicare Claims

Vascular Access Arena: Challenges, Progress, and Prospects

J Am Soc Nephrol 32: 2021

of the 55,727 CVC-dependent HD patients (mean age 67.8, 45% female), nearly 29% (n=15,882) developed a CRBSI (median time, 69 days); 54% (n=8,393), 67% (n=10,327), and 80% (n=12,705) occurred within 90, 180 and 365 days of CVC insertion, respectively. After CRBSI occurrence, 40% and 50% died within 60 days and 180 days, respectively. CRBSI patients also had a significantly lower median survival (25.1 vs. 37.3 months) compared to non-CRBSI patients [hazard ratio: 0.74, 95% CI: 0.71-0.76].

Conclusions: CRBSI is a major complication that results in higher mortality risk and shorter survival. A CVC control group was identified by an assigned index date (i.e., CVC insertion date + median time to CRBSI). Patients with CRBSI had a higher risk of death compared to patients without CRBSI; with a 40% mortality within 60 days post-CRBSI.

Funding: Commercial Support - Cordex

PO1025

Vascular Access in Kidney Transplant Patients with Allograft Failure Returning to Hemodialysis

Molly Fisher,1 Anirudh R. Gone,1 Linda Mathew,1 Crystal K. Johnson,1 Enver Akalin,1,2 Michele H. Mokrzycki,1,2 Tanya S. Johns,1,2 Montefiore Medical Center, Bronx, NY; 2Albert Einstein College of Medicine, Bronx, NY.

Background: Central vein catheters (CVC) are the predominant vascular access (VA) in incident hemodialysis (HD) patients and are associated with worse outcomes compared to arteriovenous (AV) access. Limited data exist on VA type and association with outcomes in kidney transplant recipients (KTR) with allograft failure. We aimed to determine factors associated with VA type among KTR with allograft failure who return to HD.

Methods: We performed a retrospective study of 147 KTR >18 years with allograft failure between 2010-2021 at an academic hospital in the Bronx, NY. KTR with immediate allograft failure or <1 month of HD following allograft failure were excluded. Data was collected on pre-transplant dialysis modality, vintage, and VA type. Data at allograft failure included sociodemographics, comorbidities, clinic visits, VA type. Descriptive analyses and logistic regression were performed to evaluate factors associated with VA among KTR who return to HD.

Results: At allograft failure, mean age was 53 years (SD 15), 62% were men and 46% were of Black race. Pre-transplant, 91.8% patients were on HD; 2.7% were on peritoneal dialysis (PD), and 5.5% were not on dialysis. Mean vintage was 4.6 years (SD 4.4). Pre-transplant VA included AV access in 87.7% and CVC in 4.1% of patients. At allograft failure, 82.3% and 17.7% KTR initiated HD with an AV access and CVC, respectively. Compared to pre-transplant HD patients, those on PD or who received a preemptive transplant were less likely to initiate HD with an AV access at time of allograft failure (80.6% vs 50% vs 12.5%, p<0.001). KTR were 19% less likely to initiate HD with an AV access for each year increase between the time of transplant and allograft failure (OR 0.81, 95% CI 0.69-0.94). Sociodemographics, comorbidities and number of clinic visits 1 year prior to allograft failure were not associated with VA. One year mortality was 10.7% in KTR initiating HD with a CVC vs 3.4% in those with an AV access (p=0.12).

Conclusions: The majority of KTR with allograft failure returned to HD with an AV. CVC use was higher in those with longer allograft survival, previously on PD or who received a preemptive transplant, highlighting a need for transition of care optimization. Larger studies are needed to determine if VA type is associated with mortality in this population.

PO1026

Abstract Withdrawn

PO1027

Reusing Occluded Veins: Inside-Out Central Venous Access for Hemodialysis, Our Institutional Experience

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Background: Central venous occlusion is a challenge in end-stage renal disease (ESRD) patients dependent on hemodialysis. The inside-out central venous access (IOCV) procedure is an established method of re-using occluded central veins.

Methods: Retrospective single-center study examining characteristics of patients with ESRD who underwent IOCVA between 01/01/2017 – 05/01/2021. All procedures were performed with moderate conscious sedation by an interventional cardiologist or nephrologist.

Results: 46 IOCVA procedures were performed in 39 ESRD patients. All procedures were performed to re-use the occluded right internal jugular vein (RIJ) for tunneled dialysis catheter placement. Mean patient age was 58 ± 14.6 years. 20 (51.3%) patients were male. Hypertension and diabetes were comorbid conditions in 29 (74.4%) and 20 (51.3%) patients, respectively. A total of 7 (17.9%) patients had prior kidney transplant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO1029

Machine Learning for Prediction of Arteriovenous Fistula Failure
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Background: Vascular access aneurysms are a frequent finding in hemodialysis patients with arterio-venous (AV) fistulas and grafts. Of great concern is aneurysm rupture that may result in fatal hemorrhage. To that end we used artificial intelligence (AI) to automatically evaluate vascular access aneurysms.

Methods: We collected images of a diverse range of AV vascular accesses using mobile devices. Vascular access experts adjudicated the images and diagnosed the severity of AV fistula and graft aneurysms. We then randomized the images for training (70%) and validation (30%). We trained a convolutional neural network (CNN) utilizing Amazon SageMaker platform. CNN performance was measured by the area under the receiver operating characteristics (ROC) curve in the validation images.

Results: We collected 1,341 AV access images in patients dialyzed in 20 Renal Research Institute clinics in six U.S. states. The adjudication of images identified 1,093 not advanced and 248 advanced aneurysms; examples are shown in Figure 1. With the validation images, we achieved an area under the ROC curve of 0.96. Considering different probability threshold for advanced aneurysm, if threshold is 0.37, we achieved sensitivity of 80%, specificity of 95%, false positive rate of 5%, precision of 79% if threshold is 0.7, specificity of 66%, specificity of 99%, false positive rate of 1%, precision of 92%.

Conclusions: Our solution of applying advanced AI technologies achieved very high sensitivity, specificity, precision, and a low false positive rate. The CNN could assist the clinician with actionable information and improve clinical outcomes.

Funding: Commercial Support - Fresenius Medical Care North America
Severity of AV access aneurysms. Panel A shows the images from 6 patients with not advanced AV aneurysms. Panel B shows images from 6 patients with advanced AV aneurysm.

PO1031
Evaluation of a Wearable Device for Continuous, Noninvasive Monitoring of Hematocrit Levels in Hemodialysis Patients

Background: Maintenance of euvelumia is a major challenge for hemodialysis patients, who account for a combined 6.5M annual hospital days. Clinical outcomes could be improved, and healthcare costs lowered, by enabling better management of fluid status and anemia, which is common among ESRD patients. This study presents a novel wearable device, SmartPatch, that uses multi-wavelength photoplethysmography (PPG) and other sensors to measure blood hematocrit (Hct), a key metric for monitoring fluid status and anemia. The SmartPatch is a component of a novel Remote Monitoring System (RMS) that facilitates secure data transmission and analysis and generates actionable alerts. Data demonstrating the feasibility of the RMS were previously presented at Kidney Week 2019 (Kuraguntla et al.). The aim of this study was to evaluate the system’s ability to accurately and precisely measure Hct in a real-world dialysis setting.

Methods: 14 ESRD patients with arteriovenous fistulae currently undergoing dialysis were recruited to participate in this study. Each of these patients had a SmartPatch device placed on the skin over their fistula at each of three dialysis sessions two weeks apart. Reference Hct measurements were taken immediately before and after the session, times to coincide with SmartPatch data recordings. A total of 83 sets of multi-channel PPG data were recorded and analyzed to determine the accuracy and precision of Hct measurement.

Results: The RMS measured Hct with root-mean-square error (RMSE) of 2.13 Hct compared to reference values obtained from a Sysmex XN-1000 blood analyzer. The standard deviations for each read on the same patient—with the same device—were computed and averaged, weighted by group size, as a measure of precision. The RMS measured Hct with a mean standard deviation of 1.15 Hct. These error and standard deviation values compare favorably to available point-of-care devices like the HemoCue Hb 201++, which has been reported to measure Hct with a mean of 4.32–4.81 Hct and standard deviation of 1.56–3.88 Hct.

Conclusions: The results of this study illustrate the ability of the wearable SmartPatch to non-invasively measure blood Hct in ESRD patients with AV fistulae, to a degree of accuracy and precision that may outperform available point-of-care methods. This study also demonstrated the efficacy of the end-to-end Remote Monitoring System.

Funding: Commercial Support - Allo, Inc.

PO1032
Impact of a Change in Vascular Access Flow Volume After Percutaneous Transluminal Angioplasty on Cardiac Function
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Background: Vascular access (VA) is necessary for patients on hemodialysis, and percutaneous transluminal angioplasty (PTA) is a useful treatment for maintaining VA function. PTA immediately increases the VA flow volume, which can affect cardiac function. We investigated the relationship between changes in VA flow volume and cardiac function in patients who underwent PTA.

Methods: This was a single-center retrospective observational study, including patients who underwent PTA between June 2016 and August 2016. VA flow volume and cardiac function were measured by sonography before and 1 hour after PTA.

Results: This study included 50 PTA procedures in 50 cases. PTA significantly increased the median VA flow volume from 445 (range, 150–1229) to 725 (350–1268) mL/min. Although the ejection fraction and diameter of the inferior vena cava were unchanged, the cardiac output (CO) and cardiac index increased significantly in most cases. Surprisingly, the CO was obviously decreased in 18% of cases despite the increased VA flow volume. In this atypical group, a high CO before PTA was found to be a significant factor for the decrease in CO by PTA.

Conclusions: In most cases, both VA flow volume and CO were increased by PTA, whereas in some cases, the CO was decreased despite increase in VA flow volume. This atypical phenomenon may be due to the insufficient adaptive response in the peripheral artery and heart and could predict risks for future cardiac events. Therefore, it is important that such patients are carefully followed up.

PO1033
Predicting Arteriovenous Graft Failure with Sound Signatures in Patients on Hemodialysis
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Background: The fast-growing prevalence of end stage renal disease leads to an increasing number of patients requiring dialysis worldwide. Specifically, patients on hemodialysis face the problem of maintaining their vascular accesses. Unfortunately, occurrence of stenosis and clots is not uncommon, especially in arteriovenous grafts (AVG). Graft longevity can be improved by effectively detecting and preventing these circumstances. The aim of this study is to develop a portable recording device that detects stenosis by extracting information from blood flow sounds.

Methods: Blood flow sounds were collected at four different locations on the arm, including venous and arterial ends of arteriovenous access. Measurements were conducted weekly, with four minute-recordings per patient. A logistic regression model is used to analyze sound data. Recordings obtained prior to percutaneous transluminal angioplasty (PTA) procedures were labeled abnormal and those after PTA were labeled normal. Extracted features from each labeled recording include energy, spectrum, mel-frequency cepstrum, and chroma, as shown in Figure 1.

Results: In total, we have 109 labels, 25 of which are abnormal cases. Note that each case contains 4 separate recordings. For evaluation purposes, we randomly chose 75% of the labels as training cases and used the rest as testing cases. Each random trial compares single-location detection models to one integrated model, which combines data from all four locations. The trial was repeated 100 times. Our results in Table 1 indicate that arterial sounds are more informative than venous sounds in detecting stenosis. Note that the integrated model also significantly outperforms the other single-location models.

Conclusions: Our proposed model shows excellent performance in screening for AVG failure. This algorithm has potential to provide reliable and reproducible detection of vascular access abnormalities, optimizing AVG outcome and management for clinicians and patients.

Funding: Clinical Revenue Support

PO1034
A Novel Method for Ligation of Accessory Veins: A Case Series of Eight Patients
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Introduction: Accessory veins are a common cause for decreased blood flow through the body of arteriovenous fistulae (AVF). A common practice is to have these ligated surgically through a cut-down procedure. Alternatively, these can be blocked by coiling, embolization, or by percutaneous ligation. We present a case series where accessory veins were ligated percutaneously under direct ultrasound (US) visualization.

Case Description: A total of 8 patients underwent percutaneous accessory vein ligation from Dec 2020 through May 2021. None had any immediate complications. Occlusion of blood flow through the accessory vein was confirmed by color doppler ultrasonography and by angiography. Technique description: After identifying the accessory vein on angiography and its impact on the flow through the AVF, the vein is then identified using the US. The location to ligate the vein is then chosen as close as possible to the vein “take-off”. Using a 4-0 absorbable suture and under direct US visualization, the needle is inserted from one side of the vein and passed underneath to come out from the other side. Then, the needle is flipped and inserted back subcutaneously, passing above the vein to come out eventually next to the initial insertion site. The suture is then tied firmly. Depending on the size and location of the vein, another suture can be done in a similar fashion a few millimeters away. Color doppler is then used to detect any flow through the vein. Confirmation of the cessation of flow can also be achieved by repeat angiography.

Discussion: Percutaneous ligation of the accessory veins is a technique that saves the patients from undergoing an open surgical intervention. Utilizing the US for direct visualization of the needle during the procedure enhances its safety and efficiency.
PO1035

Feasibility of Treating Stenotic Fistula Lesions with a Drug-Coated Balloon Prior to Using a Standard High Pressure Balloon
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Background: Hemodialysis access maintenance is a major cost expenditure for dialysis care. Patients often require multiple procedures per year, often treating the same access lesion in a AVF / AVG. A large proportion of stenotic lesions develop secondary to neointimal hyperplasia. Standard treatment has been angioplasty using high pressure non-compliant balloons. Recently drug coated balloons (DCB), coated with the medication paclitaxel, to help decrease neointimal hyperplasia, have been used in dialysis access treatment. The safety profile and efficacy have been proven to decrease lesion reoccurrence at 6 months when compared to regular angioplasty. Traditionally the recommendation for use of DCB is to follow after the lesion has been primarily dilated with a high-pressure balloon (HPB).

Methods: For DCB use the manufacture recommends pretreatment of the lesion with a HPB followed by secondary DCB treatment. This Arthur decided to modify the technique and treat lesions needing angioplasty with DCB first (example in figure 1) and only secondary treatment with HPB if there was not sufficient resolution of the lesion / balloon inflation to achieve less than 50% residual stenosis. Observational data is being tracked for patients undergoing fistulograms to provide a single center observational prospective cohort to look into this issue.

Results: Currently 11 patients with 15 total lesions have undergone this modification of treatment in the past 9 months, with 3 of the 11 patients having repeat fistulograms post treatment. Nine of the 11 patients required no HPB follow up. One of the 11 patients suffered a cephalic arch rupture and required stent graft placement.

Conclusions: Early data from this observational study shows that treatment of a stenotic lesion using a DCB as the only treatment is effective in the majority of cases to achieve full lesion angioplasty. Preliminary results indicate no change in long term efficacy in the DCB lesion treatment.

PO1036

Predictors of Vascular Access Thrombosis in Maintenance Hemodialysis Patients: An Historic Cohort Study
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Background: Vascular access (VA) thrombosis is a known complication in patients with end-stage kidney disease on hemodialysis (HD), but its risk factors are not completely established. We performed a study with the aim of ascertaining risk factors for VA thrombosis.

Methods: A multicenter retrospective cohort study was performed in three HD units to determine VA thrombosis rate and associated risk factors in maintenance HD patients, from July 2019 to April 2021. Descriptive statistics were calculated and expressed as median (IQR) or count (%). Univariate and multivariate logistic regression was used to calculate the adjusted odds ratio (aOR) with 95% CI for the variables associated with VA thrombosis.

Results: From a total of 178 maintenance HD patients, there were 30 (16.9%) VA thrombosis during follow-up. Our cohort had a median of 71 years (61-80), 59.6% (n=106) were male, were on HD for a median of 63.52 months (37.58-98.87), 37.6% (n=67) had diabetes, 66.1% (n=107) cardiovascular disease and 35.6% were on anticoagulant or antiplatelet agents. As to the VA, 87.1% (n=155) had arteriovenous fistulas (AVFs) and 28.1% (n=50) had history of previous percutaneous or surgical interventions. When comparing cases that led to thrombosis to VAs that maintained patency, thrombosis was more likely in arteriovenous grafts (AVGs) versus AVFs (60.9% vs 19.3%, p< 0.001), in VAs that had previous percutaneous or surgical interventions (34% vs 10.2%, p<0.001), had a VA flow (Qa) slope ≥ 25% or Qa value < 500ml/min, excluding radiocephalic AVFs (30.4% vs 11.7%, <0.001) and those with spKt/V < 1.4 (40% vs 11.2%, p<0.001). Multivariate analysis risk factors independently associated with VA thrombosis were AVFs [aOR 13.35 (4.38-40.74), p<0.001], Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs [aOR 5.00 (1.76-14.18), p<0.003], and spKt/V <1.4 [aOR 8.23 (2.90- 23.35), p<0.001]. The model had a Nagelkerke R2 of 42.1%, Hosmer-Lemeshow goodness-of-fit test performed well (χ2= 0.215, df=3, p=0.975) and showed very good discrimination ability [AUROC 95% CI 0.85 (0.77-0.94)].

Conclusions: Our study showed AVGs, Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs, and spKt/V < 1.4 were independent predictors of VA thrombosis. Interestingly, patients’ demographic characteristics and comorbidities were not associated with VA thrombosis.

PO1037

Efficacy and Safety of Plastic Cannulae Compared with Metal Needles in the Initial Use of an Arteriovenous Fistulae in Incident Hemodialysis Patients: A Randomized Controlled Study
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Background: Successful cannulation of an arteriovenous fistula (AVF) is important in patients starting hemodialysis (HD). Metal needles have been used for decades, but the usefulness of plastic cannulae has recently been demonstrated as a new technique.

Methods: As a prospective, randomized study, eligible patients were randomized into two groups in a 1:1 ratio (n=45/group). Maturation of the AVF was confirmed using Doppler ultrasound. The primary endpoint was the initial cannulation failure rate, defined as the failure of successful completion of three consecutive dialysis sessions. The secondary endpoints were time for hemostasis at the end of HD, degree of patients’ pain, degree of cannulation difficulty felt by the nursing staffs, and achieving optimal HD adequacy.

Results: The mean time from AVF creation to the first cannulation was 48.1±16.7 days. A total of 17 cases of cannulation failure occurred, and the failure risk tended to be higher in the metal needle group than the plastic cannula group (HR 2.6, 95% CI 0.95-7.41) after adjusting for age, gender, comorbidities, and location. The overall incidence of vessel injury was higher and time for hemostasis was significantly longer in the metal group than the plastic group. The use of plastic cannula was associated with better HD adequacy compared to metal needle. However, the patients’ pain score (P=0.004) and nursing staff’s cannulation difficulty score (P=0.084) were higher in the plastic group, emphasizing the great importance of practice using plastic cannula.

Conclusions: The vascular outcomes of plastic cannulae were much favorable compared to metal needles in incident HD patients. The use of plastic cannulae could be a new and innovative way to improve the quality of dialysis.
Vascular Access Arena: Challenges, Progress, and Prospects

Conclusions: While patients and providers identified common perspectives related to the nature and timing of the vascular access decision, conflicting priorities and preferences may impact the decisional outcome. This study highlights opportunities to address decisional conflicts and enable shared decision making in vascular access selection.

Vascular Access Selection Among People Receiving Hemodialysis: A Qualitative Study of Shared Decision-Making
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Background: Vascular access decision processes have been receiving increased attention; however, the extent to which these decisions are made is unclear. We aimed to explore how such decisions are made from the perspectives of patients, their caregivers, and their healthcare providers.

Methods: This qualitative descriptive study used purposively sampled patients receiving maintenance hemodialysis via an arteriovenous fistula or central venous catheter, their informal caregivers, and their healthcare providers. We conducted semi-structured interviews by telephone or in person with 19 patients, 2 caregivers, and 21 healthcare providers (8 nephrologists, 7 hemodialysis nurses, 6 vascular access nurses). We coded transcripts in duplicate and generated themes through an inductive, thematic analysis approach.

Results: Participants described a decisional hierarchy, whereby decisions regarding vascular access were predicated on upstream decisions (i.e., dialysis initiation, transplantation, home dialysis) that were preference sensitive and prioritized over vascular access type. Upon reaching a decision for hemodialysis, vascular access decision making was influenced by the following: 1) preferences for kidney replacement therapy, including anticipated timeline to transplantation or transition to home dialysis modalities; 2) urgency and timing of dialysis need, where urgent patients expressed preferences; 3) limitations of individualized decisions, as when preferences and practicalities diverged; 4) occasions to re-visit the vascular access selection; and 5) availability of support for vascular access decision making and the decisional outcome.

Conclusions: Although patients and caregivers prioritized upstream decisions, several influences on vascular access decision making were identified once the decision for hemodialysis was made. These findings can inform approaches to integrating shared decision making in dialysis and vascular access selection.
Feasibility of Creation of an Endovascular Arteriovenous Fistula in Patients Undergoing Preoperative Vascular Mapping

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Background: The endovascular arteriovenous fistula (endoAVF), a novel percutaneous technique of AVF creation, was approved by the Food and Drug Administration in 2018, and has been placed in a small number of U.S. hemodialysis patients. It is unknown how often patients with advanced chronic kidney disease have vascular anatomy suitable for endoAVF creation. The goal of the present study was to determine the proportion of patients with a vascular anatomy suitable for endoAVF creation, and to assess patient characteristics associated with such suitability.

Methods: All patients referred for vascular access placement at a large academic medical center underwent standardized preoperative sonographic vascular mapping to assess suitability for an AVF. During a two-year period (March 2019 to March 2021), we assessed the suitability of the vessels for creation of an endoAVF. We then compared the demographic characteristics, comorbidities, and vascular mapping measurements between patients who were or were not suitable for an endoAVF.

Results: During the study period, 233 patients had preoperative vascular mapping results suitable for creation of a surgical AVF. Of these, 140 (63%) were also suitable for an endoAVF. Patients with a vascular anatomy suitable for an endoAVF were younger (age 55 ± 15 vs 60 ± 14 years, p < 0.01), but similar in sex, race, diabetes, hypertension, coronary artery disease, and peripheral artery disease.

Conclusions: Among patients with chronic kidney disease with vascular anatomy suitable for a surgical AVF, 63% are also suitable for an endoAVF. Older patients are less frequently suitable for an endoAVF.

Funding: NIDDK Support

Endovascular Arteriovenous Fistula Closure with Covered Stent Placement


Introduction: WavelInQ™ endovascular arteriovenous fistula (EndoAVF) system is a new technique that uses radiofrequency energy to create AVF. It has been gaining popularity as it avoids major surgery, has less recovery time and better success rates than surgical AVF creation. Pseudoaneurysm, dissection of brachial artery, intra-procedure brachial artery thrombosis, device embolization, and steal syndrome are described complications of the procedure. We present a case of EndoAVF creation complicated with forearm swelling and its successful management.

Case Description: Patient is a 45 y/o male with End-Stage Renal Disease due to Hypertensive Nephrosclerosis and obstructive uropathy, now s/p failed kidney transplant, currently on Peritoneal Dialysis (PD). PD was failing and decision was made to transition patient to hemodialysis (HD). In preparation of HD, AVF using WavelInQ EndoAVF system was placed in right forearm between intramuscular artery and vein with coiling of the medial brachial vein. A week after fistula creation, patient developed right forearm swelling with numbness and tingling. Fistulogram demonstrated stenosis in the perforator vein with poorly developed cephalic vein and diversion of blood flow to multiple superficial collateral veins in the forearm causing swelling. Multiple attempts at balloon assisted maturation of the cephalic outflow were unsuccessful. Due to persistent forearm swelling with discomfort a decision was made to close the fistula. A 5 x 15 mm self-expanding Viabahn™ stent was deployed in interosseus vein across the anastomosis to close the fistula. Post fistula closure, arm swelling resolved completely.

Discussion: Covered stents have been used in the maintenance of hemodialysis AVF for various purposes including dialysis access stenosis, central vein stenosis, pseudoaneurysm exclusion and angioplasty associated vascular rupture that cannot be repaired using balloon catheter. This is the first reported case of successful use of covered stent graft to occlude anastomosis to close EndoAVF. As these fistulae are created more often, more novel complications will be encountered. It will be imperative for interventionalists to find creative solutions as well as actively report the successful management of complications.

Arteriovenous Access Creation and Re-Intervention Before Starting Hemodialysis

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Background: Patients with systemic lupus erythematosus (SLE) have a higher risk of vascular complications.

Methods: This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of interventional after vascular access creation. This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of intervention after vascular access creation.

Results: Totally, 1366 HD patients with SLE had higher incidence rates of AVF/AVG dysfunction than 4098 non-SLE HD patients in the following 4 periods, (1) after 1 year (incidence rates were 15.21% and 13.01% respectively; subdistribution hazard ratio (SHR) = 1.16; P = 0.007), (2) 1st-to-10th-year period (15.36% and 13.25%; SHR = 1.16; P = 0.007), (3) 5th-to-10th-year period (11.91% and 8.1%; SHR = 1.42; P = 0.003), and (4) overall period (23.53% and 21.66%; SHR = 1.13; P = 0.027). There were significantly higher incidence rates of AVF/AVG dysfunction in SLE patients during the long-term follow-up period.

Conclusions: In conclusion, regular surveillance of vascular access function by clinical examination after 1 year, especially during 5 to 10 years, is needed to improve vascular access patency and dialysis adequacy in SLE patients undergoing maintenance hemodialysis.
Results: Median age was 71 years, 64% were men, 43% had diabetes, and 33% started hemodialysis urgently. Half (51%) underwent a first arteriovenous access creation: a fistula in 21,240 patients, created a median of 5 months (IQR, 2-12), and a graft in 741 patients, 3 (1-8) months before hemodialysis initiation. Among patients with a first fistula attempt, 30% underwent at least one vascular access re-intervention before hemodialysis initiation, versus 21% among those with a first graft attempt (p<0.001). The types of intervention substantially differed according to vascular access (Figure). When dialysis start was urgent, catheter was used in 43% of patients from both access groups (p=0.06); when it was not, catheter was used in 12 and 14% of patients with a first fistula or graft attempt, respectively (p=0.15).

Conclusions: In incident hemodialysis patients in France, fistula is typically the first attempted arteriovenous access. Early arteriovenous access creation prevents from using catheter at dialysis initiation in a majority of patients, but requires close monitoring of potential complications.

Funding: Government Support - Non-U.S.

PO1045
Incidence of De Novo Central Vein Stenosis in Hemodialysis Patients Following Their First Tunneled Central Vein Catheter (CVC) Placement
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Background: Central vein stenosis is a common complication in hemodialysis patients following tunneled CVC insertion. Little is known about its incidence, association with patient characteristics, or relationship with duration of CVC placement. We systematically evaluated central vein stenosis in hemodialysis patients receiving their first CVC at a large medical center.

Methods: All new hemodialysis patients underwent an ultrasound prior to their internal jugular tunneled CVC placement, to exclude venous stenosis or thrombosis. If they were subsequently referred for CVC exchange, a catheterogram/venogram was performed to assess for hemodynamically significant (≥50%) central vein stenosis. During a five-year period (January 2016 to January 2021), we quantified the incidence of central vein stenosis in patients undergoing CVC exchange. We also evaluated the association of central vein stenosis with patient demographics, comorbidities, and duration of CVC dependence prior to exchange.

Results: During the study period, 273 patients underwent exchange of a tunneled internal jugular vein CVC preceded by a catheterogram/venogram. Of these, hemodynamically significant central vein stenosis was observed in 36 patients (13%). Central vein stenosis was not associated with patient age, sex, race, diabetes, hypertension, coronary artery disease, peripheral artery disease or CVC laterality (Table 1). The frequency of central vein stenosis was progressively higher with greater duration of CVC dependence, being 10%, 12%, 24%, and 28% in patients with <3 months, 3 to 6 months, 6 to 9 months and >9 months of catheter dependence, respectively (p=0.025).

Conclusions: Among incident hemodialysis patients receiving their first tunneled internal jugular CVC, the overall incidence of hemodynamically significant central vein stenosis was 13%. The likelihood of central vein stenosis was directly associated with the duration of CVC dependence.

Funding: NIDDK Support

PO1046
Hospitalization Risk and Long-Term Complications Associated with Catheter-Related Bloodstream Infection Among Hemodialysis Patients
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Background: Central venous catheters (CVC) are frequently required for vascular access in hemodialysis (HD) and are commonly associated with catheter-related bloodstream infections (CRBSIs). CRBSIs may have devastating consequences leading to increased hospitalizations, and long-term complications such as stroke, myocardial infarction (MI), heart failure (HF), and endocarditis, among others. This analysis explores the risk of CRBSI-associated hospitalizations and long-term complications among HD patients.

Methods: A 1:1 propensity score matched case-control analysis was conducted using merged data from United States Renal Data System (USRDS), CROWNWeb (dialysis organizations), and Medicare claims database (2013-2017). All CVC-dependent HD patients from 2014-2016 with a 1-year pre- and ≥1-year post-index period were included. CRBSI was defined as a composite measure of its ICD codes or sepsis/bacteremia diagnosis with hospitalization or without occurring pneumonia, gangrene, or urinary tract infections and hospitalization. An assigned index date (i.e., CVC insertion date + median days to CRBSI reported in CRBSI-case group) was used to identify non-CRBSI patients. CRBSI/non-CRBSI group differences were described using frequency, mean, median, chi-square, and t-tests. At 1-year post CRBSI, adjusted differences in hospitalizations and hospital days and time to long-term complications were modeled using generalized linear models with proportional hazard models, respectively.

Results: CRBSIs result in higher 1-year incremental rates of: stroke (6.6%), MI (9.2%), HF (13.4%), PVD (13.6%), and endocarditis (9.4%). Mean number of hospitalizations and hospital days were 3.79 and 25.0 days for CRBSI, and 1.96 and 5.86 days for non-CRBSI patients, respectively. Mean hospitalizations and hospital days were significantly higher for CRBSI vs. non-CRBSI patients (p<0.05) at 1-year post-CRBSI. Hazard ratios for CRBSI patients were: stroke (1.64, 95% CI 1.53-1.75), MI (2.56, 95% CI 2.37-2.78), HF (2.01, 95% CI 1.88-2.14), and endocarditis (13.42, 95% CI 10.97-16.42).

Conclusions: Results show HD patients with CRBSIs incur a significant morbidity burden due to increased hospitalizations, hospital days, and long-term complications such as stroke, MI, HF, PVD, and endocarditis.

Funding: Commercial Support - Cormedix

PO1047
Hemorrhagic Shock due to Cutting of the Tunneled Dialysis Catheter
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Introduction: Bleeding is a relatively rare complication of dialysis CVC overall. To our knowledge, this is the first report of a cut tunneled CVC proximal to the Y. This case demonstrates the risk of significant hemorrhage when a tunnelled CVC is damaged at this location and need for early recognition and control of bleeding. It also highlights important patient safety considerations given the risk of self-inflicted trauma in patients with dementia and language barrier for communication.

Discussion: Case Description: We describe the case of a 68-year-old non English speaking dementia patient with ESRD on HD. While in hospital, he had tried to cut the tape that was causing itching, but accidentally cut CVC. He was found in shock, bleeding from the exit site, which required aggressive resuscitation and compression to stop bleeding. After stabilisation examination revealed a palpable, well retracted catheter that was not visible (Fig 1). X ray showed the catheter in situ, but the Y along with the arterial and venous ports were absent (Fig 2). In retrospect, bleeding was particularly difficult to control because the cuff at this location is rigid and not compressible. This places the patient at increased risk for exanguination leading to hemorrhagic shock, air embolism and mortality.

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**PO1048**

**Facial Swelling: Angioedema or Superior Vena Cava (SVC) Syndrome**

**Moarj A. Qazi,1 Huma Qazi,2 Anne M. Huml,1 Tushar J. Vachharajani.1**

1Cleveland Clinic, Cleveland, OH; 2Army Medical College, Rawalpindi, Pakistan.

**Introduction:** Central venous stenosis is a common complication of recurrent central venous catheters (CVCs). Diagnosis can be challenging given its versatile presentation. Facial, unilateral breast or upper extremity swelling and signs of congestion mimicking pulmonary edema can be subtle clues. We describe a case of SVC syndrome that eluded clinicians as angioedema.

**Case Description:** 55-year-old female with history of morbid obesity, CKD 4, recurrent bacteremia, endocarditis and anemia presented with 1-day history of facial and oropharyngeal swelling, requiring intubation for airway protection. She was unsuccessfully treated for presumed angioedema with steroids, H2 blocker and C1 esterase inhibitor. She deteriorated, requiring tracheostomy tube, dialysis and then transferred to our hospital. She had episodes of worsening facial swelling, drooling and dyspnea with dialysis. Her medical records revealed multiple infections of her more than 10 CVCs placed in the past 12 years for frequent IV draws, infusion infections and antibiotics. Six portacaths were on the right side including 3 in subclavian, 1 in internal jugular vein and 2 peripherally inserted central catheters. A CO2 angiogram revealed stenosis of the right internal jugular, subclavian and brachiocephalic veins. The left internal jugular had the dialysis catheter with some narrowing around it. Endovascular interventions were unsuccessful at recanalization. Surgical bypass was not an option given her comorbidities. She was being evaluated for sharp or radiofrequency recanalization and/or inside-out device intervention. Unfortunately, devastated with failures, she opted for hospice.

**Discussion:** A high index of suspicion is crucial in patients with prior CVC accesses and frequent access clotting, poor flows and facial or upper extremity swelling. The number, duration and infections of CVCs increase the risk of CV stenosis. Dialysis related dyspnea, drooling or treatment resistant angioedema should be evaluated with a venogram urgently. Prompt use of advanced treatments like endovascular recanalization can be lifesaving.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**

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worsening sharp, non-radiating chest pain localized at the left hemithorax. Patient refused to move and vomiting for 2 days. Examination: a thick mucus possibly blood-streaked; however, no coffee-grounds. Stated he had never experienced this chest pain before. He reported not taking any medication at home for pain. On examination there was no cardiac murmurs, no lung abnormalities on auscultation and he had a patent arteriovenous fistula with good thrill and bruit and no signs of stenosis. Had 2 negative troponin levels with serial EKGs without ischemic changes. An echocardiogram that was negative for wall motion abnormalities or any changes in ejection fraction, ruling out an acute coronary syndrome. He had CXR showing curvilinear density projecting over the left hemithorax. He was referred to cardiology with a suspicion of metallic density adjacent to the ventricular apex. He was not on hemodialysis but before his transplant, he had multiple endovascular procedures including a stent placement to keep a patent AV access. A left upper extremity xray showed a left AV access stent fracture; findings were consistent with an embolized fragment from AVG stent. He underwent explant of the stent from AVG, but embolized fragment was not removed by CT surgery. Currently patient is chest pain free and asymptomatic.

Discussion: Stent fractures are commonly seen when they are in arteries, however this is an uncommon event in venous system specially in hemodialysis vascular access. Some of the complication associated with stent fracture are related to in-stent stenosis and central vein stenosis, but this is the first report of chest pain from stent fracture migrated to the left ventricle.

PO1052
Agitated Saline Bubble-Enhanced Ultrasonic to Visualize Appropriated Position of Hemodialysis Catheter: Does Catheter Venous Site Matter?
Gessica Sabrine Braga Barbosa, Rayra G. Ribeiro, Jorge L. Espinosa Armijos, Lucia Andrade, Igor Smolentzov, Camila E. Rodrigues. Universidade de Sao Paulo Hospital das Clínicas, Sao Paulo, Brazil.

Background: The hemodialysis non tunneled catheter (HDC) is the most common access of starting renal replacement therapy. Malposition of catheter is associated with delays in treatment. Agitated saline bubble-enhanced ultrasound (SBUS) has become a new method to visualize the HDC position. Delayed appearance of microbubbles (a 2-second) in the right atrium indicates malposition. Our objective is to analyze the accuracy of SBUS between right and left internal jugular vein (IJV) HDC insertion, comparing to chest radiography (standard method).

Methods: From December 2019 to May 2021, we evaluated 145 hospitalized patients submitted to HDC insertion in IJV. We compared SBUS with chest radiography (CR); the time spent to perform the CR, complications; patient characteristics; catheter blood flow and quality of dialysis.

Results: Total of 145 patients were analyzed, the median age was 62 years old [50.5-70], and there was no statistical difference between the site of insertion. In RIJV, 91% catheters were placed. AKI was more frequent than CKD (75% vs 25%), except when the site was LJV (46% vs 54%, p=0.05). AKI-related COVID-19 was the most common etiology (54%). The confirmation of catheter placement by SBUS was correlated with position by CR (All: r=0.6603, p<0.0001; R: r=0.7044, p<0.0001; L: r=0.6396, p=0.0769). SBUS was highly accurate in identifying adequate location of HDC, especially in R IJV (All: 97.9%; R IJV: 99.2%; L IJV: 84.6%, p<0.05). The time of the catheter insertion to perform radiography was 191 minutes [83.5-287]. Adequate syringe blood flow and an effective hemodialysis session was more frequent in R IJV catheter (99.2% vs 53.8%, p<0.05; 96.8% vs 72.7%, p<0.05, respectively). Complications occurred in 4.2%, without statistical differences between catheter sites.

Conclusions: Comparing with chest radiography, agitated saline bubble-enhanced ultrasound was more accurate in identifying adequate placement of R IJV than L IJV hemodialysis catheters.

Funding: Government Support - Non-U.S.

PO1053
Using the Seraph® 100 Microbind®Affinity Blood Filter Under Slow Flow Conditions Through a Normal Central Line
Infant-Thises Seliger, Julius Schneider, Jan T. Kielsstein.1 Kielstein Lab, Academic Teaching Hospital Braunschweig, Braunschweig, Germany; 2Medizinische Hochschule Hannover, Hannover, Germany.

Background: The Seraph® 100 Microbind® Affinity blood filter has been in use since 2019 for the treatment of difficult to treat blood stream infections and since 2020 for the treatment of critically ill COVID-19 patients. It is operated under blood flow rates of 100 – 350 mL/min, which requires a large bore central line a dialysis catheter. The aim of our study was to evaluate the usability of the Seraph® 100 under slow flow conditions through a normal central line (in clinical practice).

Methods: A standard hemoperfusion blood tubing system as well as the Seraph® 100 (Exthera Medical, CA, USA) was used. Vascular access was a 20 cm trilumen central venous line (2 x 16 G and 1 x 16 G) that was inserted into a reservoir. The Multifiltrate (Fresenius Medical Care) was used to pump normal saline (n=5) or human plasma (n=5) through the Seraph® 100. Pressures were recorded at any given flows (Qb).

Results: Using saline or human plasma the Seraph® 100 Microbind® Affinity Blood Filter can be operated at blood flow rates of up to 100 mL/min even through a 16 & 18 G lumen at tolerable arterial and venous pressures. In men using either the 12 G or the 16 G lumen as "arterial line" blood a blood flow rate of 50 mL/min could be maintained for 24 hours without problems.

Conclusions: The Seraph® 100 Microbind® Affinity Blood Filter can be operated at blood flow rates of 50 mL/min even through 16 & 18 G catheters.

PO1054
Keeping the Vascular Access Alive During the COVID-19 Pandemic

Background: Delay in care of suspected stenosis or thrombosis can increase the chance of losing hemodialysis access. Many procedures were canceled or postponed at the start of the COVID-19 pandemic. We have done a study to determine if the COVID-19 pandemic affected dialysis access care.

Methods: We performed a retrospective chart review to evaluate the incidence of both fistula and graft thrombectomies between April 1, 2020, and March 31, 2021, designated as the COVID-19 group and compared it with an incidence between April 1, 2019, and March 31, 2020, designated as the pre-COVID-19 group. Unsuccessful thrombectomy was defined as subsequent tunneled hemodialysis catheter placement within 48 hours after thrombectomy due to clotted access.

Results: There was no significant difference in the total fistula and graft thrombectomies between the two time periods: 44 cases in the pre-COVID-19 era, the incidence rate of 0.12 per patient-year; 54 cases in the COVID-19 era, the incidence rate of 0.14 per patient-year (HR=1.23, 95% CI=0.81-1.89, p=0.31). However, there was a significant increase in the fistula thrombectomy in the COVID-19 era: 9 cases in the pre-COVID-19 era, the incidence rate of 0.024 per patient-year; 21 cases in the COVID-19 era, the incidence rate of 0.037 per patient-year (HR=2.38, 95% CI=1.03-5.88, p=0.02). In addition, the incidence of unsuccessful fistula thrombectomy also increased significantly: 2 cases in the pre-COVID-19 era, the incidence rate of 0.005 per patient-year; 9 cases in the COVID-19 era, the incidence rate of 0.024 per patient-year (HR=4.54, 95% CI=1.01-50, p=0.03). There was no significant difference in total as well as unsuccessful graft thrombectomy between the two eras.

Conclusions: We noticed a significant increase in fistula thrombosis and unsuccessful fistula thrombectomy in 1-year of the COVID-19 pandemic. This could be due to a delay in referring the patients for treatment of fistula stenosis. Even though the dialysis access procedures were considered essential, there might have been hesitancy on part of patients and referring dialysis center which led to this result. However, we did not notice this trend in AV graft. Timely referral for intervention is important to prevent vascular access thrombosis and loss.
PO1055
Virtual Interviewing in the COVID-19 Era: What Have We Learned?
Koval Jain, Gerald A. Hladik, Prabir Roy-Chaudhury, Pankaj Jawa. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Background: The COVID-19 pandemic forced institutions across the US to switch to virtual interviewing. While some institutions were already offering virtual interviews on a limited basis, this was the first time all interviews were conducted using a virtual platform. Herein, we describe the experience of the nephrology fellowship interviewees at the University of North Carolina (UNC).

Methods: We distributed an anonymous Qualtrics survey to all the nephrology fellowship interviewees (N=80) at UNC. The survey included questions on quality of virtual interviews and was completed after the match to avoid bias related to the matching process.

Results: Thirty-one candidates completed the survey (39%), although not all questions were answered by everyone. The total number of interviewees increased from 41 in 2019-20 to 80 in 2020-21. 95% were satisfied with their virtual experience. 82% indicated that the virtual interview process enabled an informed decision about the fellowship program. Everyone was satisfied with the organization of the interview day (N=22). 28% responders (5/18) identified as underrepresented minority (URM). In 2019-20, 641 interviewees identified as URM as compared to 14/80 in 2020-21. The most common reasons for not ranking our program amongst the top three included limited job opportunities for partners, inability to visit the area, and lack of family in the area. Candidates valued the people they met and were able to get a feel for the program despite virtual interviews. They were particularly satisfied with the opportunity to meet fellowship faculty and residents on one platform. Interviewees specified lower cost and time efficiency as advantages of virtual interviews.

Conclusions: This is the first report of the virtual interview experience for nephrology fellowship applicants. The virtual interview process increased the applications to our program although the number of URM applications were similar compared to previous years. There was uniform satisfaction with the virtual format and interviewees were able to appreciate the culture of the division. Most applicants found the virtual interview format favorable because of reduced cost and time expenditure, enabling them to interview at more programs. Our data suggest that serious consideration should be given to a virtual platform in future years to provide opportunity and flexibility to the applicant pool and improve geographical diversity.

PO1056
“Breaking Bad News” During the COVID-19 Epidemic: A Virtual Objective Structured Clinical Examination (OSCE) for Nephrology Fellows
Mauna A. Watson,1 Anna M. Howle,2 Oliver Lenz,2 Ross J. Scalese,3 Joshua D. King,4 Jonathan A. Bolanos,5 Christina M. Yuan,6 Nephrology Education & Development Consortium1 Walter Reed National Military Medical Center, Bethesda, MD; 2University of Maryland School of Medicine, Baltimore, MD; 3University of Miami School of Medicine, Miami, FL.

Background: The “Breaking Bad News” OSCE assesses fellow counseling/communication skills in 20-minute simulation scenarios: kidney replacement therapy (KRT) in ESKD, urgent KRT in AKI, and kidney biopsy. In-person simulation was impractical during the COVID-19 pandemic, so we adapted the OSCE to a virtual platform.

Methods: The AKI scenario was audio only. Fellows called a simulated patient (SP) surrogate for urgent KRT consent. The ESKD and kidney biopsy scenarios were video encounters between fellows and SPs. Faculty observed while muted/video off. After each scenario, fellows received feedback from SPs and faculty (unmutted/video on). Fellows from 2 programs at 2 centers completed the OSCE in May 2021. Post-OSCE, fellows were anonymously surveyed about each scenario, the OSCE overall, and their estimate of the percent of outpatient encounters and inpatient KRT counseling they had done virtually in the past year.

Results: 15 fellows did the OSCE; 14 completed the survey (93% response rate). 93% rated the OSCE overall as a good/very good approximation of a telemedicine experience. 100% were satisfied very satisfied with the AKI scenario, 79% with the ESKD, and 77% with the kidney biopsy scenarios. Several commented that the AKI scenario was the most realistic—they often counseled surrogates by telephone for urgent KRT. Fellows estimated that about 25% (median 27.5%; IQR 16-50%) of counseling for acute inpatient KRT was done virtually in the past year. They estimated about 50% (median 52.5%; IQR 36-70%) of outpatient encounters were done virtually in the past year, but several (dissatisfied with the ESKD and kidney biopsy scenarios) indicated they would not have counselled similar outpatients using telemedicine.

Conclusions: Overall, fellows felt the OSCE well-approximated virtual encounters. All were satisfied with the AKI scenario. The majority were satisfied with the ESKD and Kidney Biopsy scenarios, but some did not feel they were consistent with normal practice. The OSCE allows fellows to practice telemedicine communication skills that will remain relevant post-pandemic. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Defense or U.S. Government.

Funding: Other U.S. Government Support

Figure 1: Association of Distress with Demographic Variables on Univariable and Multivariable Logistic Regression

PO1057
Well-Being of Nephrology Fellows: Evolution over the Course of a Pandemic Year
Hitesh H. Shah,1 Kurtis Pivert,2 Susan M. Halbach,1 Anna M. Burgner,4 Benjamin S. Ko,3 Lili Chan,4 Suzanne Boyle,3 Joshua S. Waitzman,2 Stephen M. Sozio,1 Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; 2American Society of Nephrology, Washington, DC; 3Seattle Children’s Hospital, Seattle, WA; 4Vanderbilt University Medical Center, Nashville, TN.

Background: We sought to assess changes in well-being of nephrology fellows over the first year of the COVID-19 pandemic in the U.S.

Methods: The Resident Well-Being Index (RWBI), a validated tool assessing physician distress, was distributed as part of ASN’s annual nephrology fellow survey to 920 current adult, pediatric, and adult/pediatric fellows. An RWBI > 5 (range 0–7) indicated distress. Demographic and fellowship factors associated with meeting the distress threshold were evaluated in univariable and multivariable logistic regression.

Results: A total of 511 fellows participated (56% response), of whom 463 completed the RWBI instrument. After 1 year of the COVID-19 pandemic, there were a higher proportion of nephrology fellows meeting the RWBI distress threshold—22% in 2021 versus 15% in 2020. Female nephrology fellows had higher RWBI scores (median 3 [IQR 3] versus their male colleagues (median 1 [IQR 3]). Higher proportions of 1st-year fellows (50% vs 42% for 2nd years, OR 0.91 [95% CI 0.76–1.09], p=0.024) and women (27% vs 18% of men, OR 1.71 [95%CI 1.06–2.76], p=0.028) met the distress threshold (Figure 1). There were no significant differences by race, ethnicity, medical school location, or adult vs pediatric fellowship. Despite the higher proportion of distress overall, 88% of respondents would recommend nephrology to medical students and residents.

Conclusions: Our follow-up assessment of nephrology fellows’ well-being after the first year of the COVID-19 pandemic indicate the continued need for supportive measures to ensure the health of the future nephrology workforce, especially among 1st year and women trainees.
Methods: Each of the 6 nephrology fellows filled out a daily survey between November 9, 2020 and January 31, 2021, which was the peak of the COVID-19 pandemic in Wisconsin to address: 1) the total amount of sleep hours 2) quality of sleep (restful or fragmented) and 3) whether on-call fellow reported to hospital from home. Responses were collected the following morning to decrease recall bias.

Results: Over the 3-month study period, 100% of the call night data was recorded. The average amount of sleep per night was 5.3 hours. When necessary to report, the average hours of sleep dropped to 4.3 hours. However, if not called in, sleep increased to 5.8 hours per night. The percentage of nights requiring patient evaluation by coming to the hospital overnight was 50% during the study period with a range of 48% of nights in December and 61% in January. Sleep during night call was described as 55% restful vs. 45% fragmented.

Conclusions: This survey has generated discussion amongst fellowship leadership and current fellows regarding novel ways to improve the night call experience to maximize education and clinical experience during training as well as improve fellow wellness. It was determined that the burden of call did not detract from the fellow education enough to warrant a change to a night float system. However, it did identify changes in management processes such as the timing of labs, implementation of dot phrases, and a sleep expert discussion to improve duration and quality of sleep.

Fellows Home Call Data

<table>
<thead>
<tr>
<th>Month</th>
<th>Average Hours of Sleep (n=14)</th>
<th>Average Hours of Sleep Drop (n=14)</th>
<th>Quality of Sleep (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 9, 2020</td>
<td>5.3</td>
<td>4.3</td>
<td>55% restful, 45% fragmented</td>
</tr>
<tr>
<td>December</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Educational Tools Used by Nephrology Fellows in 2016 and 2021 (left) and Percentage 2021 Nephrology Fellows Ranking Tools as Very Effective (right).

PO1059
Shahid N. Muhammad1,2 1The University of the West of England (UWE), Bristol, United Kingdom; 2The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.

Background: Technology has allowed patients with Long-Term Conditions (LTCs) to access information through websites, portals, and Patient-centred organisations. 1) To understand, retrospectively, whether there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education.

Methods: Fourteen (14) topic tags were applied over 1-month (March and April 2020) between groups the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDRAs) (est.2014) for Kids platforms. Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection.

Results: 2,560 threads were topic tagged between two groups. For adults, educational gaps surround Renal Replacement Therapy (166 tags, 12.66%) and Lab Tests and Biomarkers (153 tags, 10.29%). For paediatrics and young groups, educational gaps include Medication and Pharmacy (148 tags, 11.80%), Renal Replacement Therapy (133 tags, 10.65%), Peer Support (125 tags, 10.01%) and Nursing (115 tags, 9.20%).

Conclusions: Online educational modules should complement CKD pathways, and be championed by wider Allied Health Professionals. This is the first UK retrospective study that examines clinically relevant educational gaps between online paediatric and adult renal cohorts close to two decades. Education is where healthcare requires investment.

PO1060
Nephrology Education Needs Assessment: Five Years and a Pandemic Later
Benjamin S. Ko,1 Rob Roe,2 Kurtis Piver,1 Anna M. Burgner,3 Joshua S. Waitzman,4 Susan M. Halbach,5 Suzanne Boyle,6 Lili Chan,7 Hitesh Shah,8 Stephen M. Sozio,9 University of Chicago, Chicago, IL: 1American Society of Nephrology, Washington, DC; 2Oregon Health & Science University, Portland, OR; 3Beth Israel Deaconess Medical Center, Boston, MA; 4Vanderbilt University Medical Center, Nashville, TN; 5Seattle Children’s Hospital, Seattle, WA; 6Temple University, Philadelphia, PA; 7Icahn School of Medicine at Mount Sinai, New York, NY; 8Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; 9Johns Hopkins Medicine, Baltimore, MD.

Background: We sought to identify how educational tools utilized in nephrology training had evolved in the past 5 years and through the COVID-19 pandemic.

Methods: Questions about educational tools were distributed as part of ASN’s annual nephrology fellow survey to 920 current adult pediatrics/fellows.

Results: 511 fellows participated in 2021 (56% response rate), compared with 377 fellows in 2016 (31% response rate). Fellows indicated that UpToDate was still the most used (82%) and most effective educational tool (66% rated it “Very Effective”); however, ASN KSAP increased in popularity (27% in 2016, 58% 2021) and was also highly rated (65% Very Effective). Use of online resource and social media increased, including both new opportunities and prior available ones such as NephIC (7% to 32%, with 46% rated Very Effective) (Figure 1). A majority of fellows (84%) rated their education as good or excellent in 2021, a percentage similar to 2016 (81%).

Conclusions: Our follow-up assessment of nephrology fellows’ educational tools found an increase in the adoption of online resources with similar effectiveness ratings as traditional resources.

PO1061
Curriculum-Based Online Education Improves Nephrologists’ Ability to Manage Hyperkalemia in Practice
Amy Larkin, Donald Blatherwick, George Boultaslis. Medscape Education, New York, NY.

Background: The goal of continuing medical education (CME) is professional growth and improved patient care. We sought to determine if series of online continuing medical education (CME) activities will improve the clinical knowledge, competence, and confidence of nephrologists related to hyperkalemia management.

Methods: The online CME curriculum consisted of 5 online activities housed on a dedicated collection page. All used repeated pairs pre-post-assessment study design was used and McNemar’s test (P<0.05 is considered significant) to assess educational effect. The last activity was a medical patient simulation that utilized tailored clinical guidance (CG), based on current evidence and expert recommendation, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user’s baseline (pre CG) decisions using a McNemar’s test to determine P values. The activities launched between March and October, 2020 and data were collected for up to 12 weeks.

Results: The education reached over 15,000 physicians, including over 1,700 nephrologists. Overall, knowledge improved by 24% (P<0.001) and competence by 4% (P=NS) (all relative improvements) by nephrologists. Specific improvements: 40% relative increase in knowledge related to impact of hyperkalemia (P<0.001) 31% relative increase in knowledge related to clinical use of potassium binders (P=0.001) 24% relative increase in knowledge related to optimizing RAAS inhibitors in patients with hyperkalemia (P<0.05) 7% relative increase in competence related to clinical use of potassium binders (P=NS). Of the nephrologists who were included, 30% (P<0.001) had a measurable increase in confidence in hyperkalemia management.

Conclusions: This curriculum demonstrates that a curriculum is effective at moving learners on the continuum for knowledge improvements to competence improvements. Some gaps remain after education. Among these learners, 49% need knowledge improvements related to minimizing RAAS inhibitors in patients with hyperkalemia and 41% related to clinical use of potassium binders. As such, further education needed in these areas.

Funding: Commercial Support - Astrazeneca

PO1062
Level of Confidence, Knowledge, and Literacy in Genetics Among US Nephrologists

Background: Increased availability of genetic tests in nephrology and at reduced costs are promising for improved patient diagnostic and clinical care. Nephrologists’ confidence, knowledge and genetic literacy are likely to impact the utilization of genetic testing (GT). Identifying gaps in nephrologists’ knowledge and confidence and preferred methods of learning are needed to develop tailored approaches to improving it.
PO1063

Mind Map, an Educational Tool for Teaching Clinical Reasoning in Nephrology: A Mixed-Method Study

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Background: Nephrology is commonly considered as one of the most complex disciplines for medical students, justifying the implementation of new educational tools. Although its relevance has been well-established, the mind map is still marginally used in medical education. The objective of this study is to assess the contribution of mind map for teaching clinical reasoning in nephrology.

Methods: Between November 2020 and April 2021, three groups of med students (4th to 6th year) were provided with a teaching program of 5 weekly sessions of 30-45 minutes focused on three topics (serum creatinine elevation/AKI, glomerular syndromes, dysnatremia), each developed through a specific mind map. The contribution of this program was evaluated by a mixed method: 1. quantitative assessment: comparison of three quiz scores respectively the day before, day after and two weeks after each learning session (paired Wilcoxon tests); 2. qualitative assessment: focus group interviews with each group at the end of the teaching program.

Results: In total, 12 med students took part in this educational experience (respectively four in 4th, 5th and 6th years). Quiz scores were significantly higher after each teaching session and overall (28.0 [26.0; 31.4], 33.0 [31.2; 36.1], 34.4 [32.4; 37.0] respectively at baseline, immediately after and after two weeks, p < 0.001) (Fig1). Moreover, focus group interviews highlighted several themes about the specific contribution of mind map (in addition to previous standard lessons): logical and intuitive tool, effective for quick knowledge transmission, promoting long-term memorization and providing a global/integrated vision of clinical reasoning in nephrology.

Conclusions: Mind map appears to be an interesting educational tool in teaching clinical nephrology reasoning to medical students.

PO1064

Improving the Management of Gout in Patients with CKD or Kidney Transplant: Effect of Online Education


Background: Gout is a chronic condition with a considerable effect on patient health and quality of life. Hyperuricemia and gout are associated with declining renal function. Recent studies have shown that renal dysfunction and kidney transplant are risk factors for gout. A study was conducted to determine if online, segmented education could improve knowledge, competence, and confidence of nephrologists regarding the management of gout in patients with chronic kidney disease (CKD) or kidney transplant (KT).

Methods: Educational design included a 45-minute video activity with slides, segmented into a series of 5 mini-lectures by different faculty covering various aspects of gout in patients with or without CKD and KT. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design with 3 knowledge questions and 1 confidence question, in which each individual served as his/her own control. A chi-squared test assessed statistical significance at the P < 0.05 level. The activity launched 9/25/2020, with data collected through 12/4/2020.

Results: The analysis set consisted of responses from nephrologists (n=89) who answered all assessment questions during the study period. Analysis of pre- vs post-intervention responses demonstrated a significant improvement in overall knowledge; average correct responses increased from 52% pre to 76% post education. Specific areas of improvement included: Treat-to-target strategy with a target of serum UA level < 6 mg/dL in patients taking urate lowering therapy (20% relative improvement, P<0.05) Starting low-dose allopurinol in a patient previously diagnosed with gout and stage 3 CKD, presenting with painful subcutaneous tophi (25% relative improvement, P<0.01) Recommending pegloticase without dose adjustment for the management of refractory gout in patients with stage 4 or 5 CKD (222% relative improvement, P<0.001) Post-education, 48% of nephrologists had a measurable increase in confidence in their ability to manage patients with CKD who may develop gout.

Conclusions: This study demonstrated the success of online, segmented, mini-lectures on improving the evidence-based knowledge, competence, and confidence of nephrologists in appropriately managing gout in patients with CKD or kidney transplant.

Funding: Commercial Support - Horizon pharma

PO1065

Development and Implementation of an Immune Suppression Toolkit to Guide Nephrology Fellow Medication Prescribing and Monitoring

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Background: There are many important considerations when prescribing high risk medications like immune suppression (IS). Informed by surveys administered to nephrology faculty and fellows, we developed a training curriculum and a concise, clinically applicable guide for IS prescription and monitoring.

Methods: A cross sectional survey was administered to nephrology faculty and fellows in November 2017 to assess perceptions, self-efficacy, and knowledge about prescribing, monitoring, and adjusting IS (12 questions with item-responses from 1=strongly agree to 4=strongly disagree). Informed by this survey we developed and implemented a toolkit (one-time training curriculum and IS reference guide) for fellows and assessed their perceptions of the toolkit using pre-and post-surveys. Results are reported using mean (SD) or N (%). We also examined the correlation of toolkit usage with self-efficacy.

Results: Twenty-eight nephrology faculty and fellows completed the baseline survey; 19 (68%) were attending physicians and 9 (32%) fellows. Twenty (71%) were men, 16 (59%) Caucasian, 11 (41%) Asian. Collectively, 19 (77%) reported prescribing IS ranging from 1 to 40 times yearly. Attending physicians exhibited higher self-efficacy in prescribing IS (1.7 [0.6] compared to 3.3 [0.8]) and both attendings and fellows strongly agreed there was a need for IS guides 1.4 (0.8) and would use them if available 1.4 (0.6). In particular, fellows strongly disagreed they understood all steps needed to use
IS (3.3 (0.8) compared to 2.3 (0.7) for attending physicians). In May 2021, 5 nephrology fellows received the IS toolkit and completed the surveys. Self-efficacy improved post-intervention from mean (SD) 3.0 (1.2) to 2.2 (1.6). All 5 fellows (100%) strongly agreed that the toolkit added value to training, provided a guide they would use and recommended the toolkit for future fellows. 

Conclusions: Nephrology faculty and fellows strongly agreed that there is a need for guides and protocols for prescribing and monitoring IS medications. Our pilot IS toolkit incorporated into nephrology fellow training was well received and improved fellow self-efficacy.

Funding: Veterans Affairs Support

PO1067

The Impact of Electronic Sign-Out Dot-Phrase and Simulation Exercises on Inpatient Nephrology Transitions of Care

James D. Alstott,1 Anand K. Ramadurai,2 Sayee Sundar Alagusundaramoorthy,2 Samantha J. Strennen,3 Laura J. Maursseter,1 Gauri Bhutani.1 1University of Wisconsin-Madison, Madison, WI; 2University of Kentucky, Lexington, KY.

Background: A fellow-led QI project was initiated in 2018 after division surveys indicated a need for change in the ongoing division transitions of care (TOC) practice. The current landscape and clinical use of POCUS in US nephrology training programs.

Methods: We developed a standardized “sign-out score” to objectively assess TOC on the EMR sign-out. We next developed and implemented a standardized electronic medical record (EMR) dot-phrase as our first QI intervention. Case-based simulation sessions highlighting TOC pearls were conducted as the second QI intervention. Pre- and Post-intervention data for sign-out score was evaluated.

Results: A total of 647 patient EMR sign outs were assessed between 2018-2021. Overall sign-out accuracy score (0-2) significantly improved with QI interventions (pre-intervention mean 0.9 [95% CI: 0.9-1.1; N=298] to 1.6 post-dot-phrase [1.5-1.6; N=220] to 1.7 post-simulation [1.6-1.8; N=129]; p<0.001). Table 1 provides details on the results of sign-out score. After adjustment for level of training, improvement in overall accuracy was independently associated with both dot-phrase (adjusted odds ratio (aOR) 7.6 [95% CI: 4.9-11.9]; p<0.001) and simulation (aOR 1.88 [1.3-2.1]; p=0.001). Although 2 sign-out score measures which were high performing pre-intervention worsened with dot-phrase implementation: anticipated changes and non-RRT management (aOR 0.15 [0.1-0.23]; p=0.001 and 0.07 [0.02-0.23]; p=0.001, respectively), improvement was seen following simulation (aOR 1.36 [0.84-2.2]; p=0.21 and 4.6 [1.74-14.5]; p=0.002).

Conclusions: A standardized EMR sign out dot-phrase and simulation exercises both improved the overall accuracy of TOC practiced in inpatient Nephrology consult service. The impact of dot-phrase alone on previously high performing TOC measures suggests the need for further optimization of dot-phrase and continuing simulation to enhance provider self-realization of important components of TOC.

Table 1: Frequency of best possible “sign-out score” before and after QI interventions

<table>
<thead>
<tr>
<th>Sign-out components</th>
<th>Pre-intervention</th>
<th>Post-dot-phrase</th>
<th>Post- simulation</th>
<th>Post- simulation</th>
<th>Overall P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resident Diagnoses (N=141)</td>
<td>16 (11)</td>
<td>72 (50)</td>
<td>90 (64)</td>
<td>90 (64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Backbone encountered (N=41)</td>
<td>41 (12)</td>
<td>81 (77)</td>
<td>82 (71)</td>
<td>82 (71)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-RRT patient disposition (N=64)</td>
<td>44 (173)</td>
<td>89 (99)</td>
<td>89 (99)</td>
<td>89 (99)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-RRT treatment (N=44)</td>
<td>84 (1730)</td>
<td>80 (990)</td>
<td>89 (990)</td>
<td>89 (990)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall accuracy (N=97)</td>
<td>97 (830)</td>
<td>97 (707)</td>
<td>97 (85)</td>
<td>97 (85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anticipated Changes (N=109)</td>
<td>109 (81)</td>
<td>86 (147)</td>
<td>74 (148)</td>
<td>74 (148)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall accuracy (N=109)</td>
<td>109 (277)</td>
<td>97 (380)</td>
<td>74 (223)</td>
<td>74 (223)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PO1069

Point-of-Care Ultrasound Training for Nephrologists: A National Survey of Nephrology Fellows

Catherine A. Moore,1 Daniel W. Ross,2 W. Charles O’Neill.1 1University of Rochester Medical Center, Rochester, NY; 2Northwell Health, New Hyde Park, NY; 3Emory University, Atlanta, GA.

Background: Despite many potential applications of PoCUS in nephrology, nephrologists have been slow to adopt this technology. The past five years have seen an increase in ultrasound training within nephrology fellowship programs, although the scope of training is unknown. We conducted a national survey of nephrology fellows in United States-based training programs. The main objective of this survey was to identify the current landscape and clinical use of POCUS in US nephrology training programs.

Methods: We surveyed post-graduate year (PGY) 4-8 trainees in US nephrology fellowship programs. Survey items were included in a broader trainee survey disseminated to all programs by the American Society of Nephrology in April, 2021. The six-item survey instrument probed attitudes toward POCUS, current use, preferred instruction format, and perceived competence.

Results: Out of 822 US nephrology fellows surveyed, 631 (76.8 %) responded. A majority of respondents were 30-34 years of age with the majority of participants graduating from international medical schools. The majority of fellows (64.6%) indicated interest in PoCUS education, with highest interest in procedural ultrasound and diagnostic kidney imaging. Only 240 (38%) of fellows reported receiving PoCUS education during training. Of the fellows who received PoCUS training, 112 of 227 (49%) reported incorporation of PoCUS at a frequency of less than monthly, with only 62 of 227 (27%) of fellows incorporating PoCUS once per week or more. 83 of 226 (36%) fellows reported receiving adequate instruction to independently perform PoCUS, and 74 of 224 (33%) reported that they expect to be competent to independently perform PoCUS by the end of training. Hands-on training, particularly with an instructor, was highly valued as a teaching technique.

Conclusions: Despite high trainee interest in PoCUS, the majority of current nephrology fellows are not receiving training in this domain and do not feel competent to independently perform PoCUS procedures. Hands-on training guided by a skilled instructor is a highly valued PoCUS teaching technique. This survey identifies a need for the development of PoCUS programs within nephrology fellowships that incorporate hands-on teaching techniques.
POI1071
Patient Navigators and Study Coordinators: A Team Approach Towards Patient Support in Decentralized Clinical Trials
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Background: COVID-19 related restrictions have accelerated adoption of decentralized clinical trials (DCT). DCTs offer increased patient flexibility via online study platforms, telemedicine and home-based nursing. DCTs reduce travel, hospitalization and in-person interactions, all problematic under COVID. Potential drawbacks exist for both patients and study coordinators, however. In DCTs, removal of study-site visits may leave patients feeling confused, unsafe, disempowered and disengaged, potentially increasing drop-out risk. While DCTs may mean increased enrollment for sites, management of novel patient pathways may prove more time-consuming for study coordinators. Crucial protocol driven events or patient concerns/questions may be missed due to complex patient tracking.

Methods: The role of the patient navigator (PN) was developed to support both patients and study coordinators in DCTs. PNs will provide culturally-appropriate psychosocial education to ensure patients feel safe, informed, and supported. PNs serve as conduits between the patient and the study site, ensuring bi-directional communication of patient progress. This unique approach is being trialed in ARENA2, a pediatric Phase III trial in primary distal renal tubular acidosis, a rare renal disease.

Results: A multi-lingual team with unique educational and counseling experience was recruited and trained on the protocol and disease. The team will provide weekly online consultations with patients to facilitate engagement as well as identify any concerns the patient may be having in home healthcare. This role will provide around-the-clock access to care and disease-related questions for both the patient and study site.

Conclusions: The concept of sponsor-driven PN team services in DCTs will offer both patients and study sites the added benefits of support.

Funding: Commercial Support - Advicenne Inc.

POI1072
Do Undergraduates Know “Nephrology?” – A Single-Site Survey of College Students
Julia M. Hopkins, Juan Carlos Q. Velez, John M. Arthur, Michael G. Janecz.
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Background: Over the past decade, Nephrology has experienced a 43% decline in fellowship applicants. A factor to choosing Nephrology could be a lack of early exposure. While studies have been conducted to explain why residents choose a specific fellowship, none have surveyed the undergraduate student population to inquire whether the name “Nephrology” was even a recognizable medical specialty compared to other medical specialties. To this end, we conducted a survey of undergraduate students at the College of Charleston (CoC) to test the hypothesis that Nephrology will rank amongst the least recognizable specialties.

Methods: 274 undergraduates at CoC responded to a survey where they were asked to select every medical specialty they recognized by name (15 real specialties/lifestyles). Demographic questions regarding sex, race, collegiate level, high school location, pre-med track, and household income were included. Differences were considered by comparing 95% confidence intervals or Chi-Square test. Spearman-Rank test was used to examine whether the number of applicants per specialty fellowship position was correlated with the proportion of responses.

Results: Out of 15 medical specialties, Nephrology ranked lowest (29%); whereas, Pediatrics (97%) and Surgery (97%) ranked highest. The fictitious specialty, “diasymptomology” was recognized least (4%). Sex, race, collegiate level, and household income were not different between those students that recognized the word Nephrology versus those that did not. Pre-med students were about twice as likely (p=0.001) to have recognized Nephrology versus non pre-med students (49% vs. 22%, respectively). There was no correlation between the proportion of undergraduate students who recognized a specific medical specialty and the number of applicants per fellowship position in 2019 (r=0.2, p=0.7).

Conclusions: Nephrology was the least recognized, non-fictional, specialty amongst undergraduates. Lack of correlation between student responses and fellowship applications, suggest that name recognition alone will not predict fellowship applicant number. The discrepancy between Nephrology and other specialties highlights a gap in name recognition at an early career stage, even amongst premedical students.

Funding: NIDDK Support

POI1070
Teaching Application of Ultrasound in Nephrology Practice in Medical Schools Using Student Peer Teaching: A Prospective, Randomized Pediatric Trial
Rainer Bässcher, Philip Gelinger, Fiona Schmitt.
Universitätsklinikum Essen, Essen, Germany.

Background: Ultrasound has become the leading diagnostic technology in pediatrics due to its high sensitivity, easy applicability and lack of invasiveness and plays critical roles in many aspects of nephrology practice. However, it is associated with a higher examiner dependent variance. Teaching ultrasound in medical schools has grown in importance over the past years, while pediatric aspects are mainly reserved for postgraduate education. Student peer teachers take on the task of lecturers at many faculties with promising results in ultrasound education.

Methods: We designed a prospective, randomized trial in a pre-post-test design for 257 4th year medical students in our pediatric classes to investigate the effectiveness of peer teaching in pediatric ultrasound. Based on an examiner independent theory. Six students were split into smaller groups and received a standardized practical training by a multiple choice progress test was performed prior and after the course. Afterwards, participants received a supporting manual (group B). All students had to measure the right kidney volume of their partners in advance to test pre-existing practical skills and were randomized to one of the two groups. The discrepancy between Nephrology and other specialties highlights a gap in name recognition at an early career stage, even amongst premedical students.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The Information Dilemma

Tejas Desai, NOD Analytics, Harrsiburg, NC.

Background: The Internet has changed search. The amount of searchable information is growing as more bytes are added/modified than deleted and the criteria by which search results are obtained has also changed. Results are not exclusively obtained by their relevance to the query. Social media search uses predictive algorithms to display results with which the user is most likely to engage (weets, likes, replies, clicks). Results that promote engagement are valued more than those pertinent to the query. Known as customized search, this strategy is obvious when 2 individuals make an identical query and receive different search results and in a different order. Customized search protocols increase engagement but at the cost of creating an information dilemma. In this dilemma, each learner is exposed to a different set of facts upon which scientific discussions are started. In order to establish a common set of facts, I created a search engine based on a standard search protocol.

Methods: NephrTwitter.com is a non-commercial search engine that identifies search results for renal cohorts close to two decades. Education is where healthcare requires investment. This study examines clinically relevant educational gaps between online paediatric and adult health professional about blood tests and investigations (25.49%). Surrounding Healthcare, highest response included I have ability to communicate with a AHPs will increasingly work with GPs to provide laboratory screening, and POCT advice Males (42.86%). Relating CKD Patients, highest responses included Females (55.00%) P1074

Understanding Healthcare Education for Nephrology Best Practice – A Question of Which Health Professionals: A Quantitative Investigation

Tejas Desai, NOD Analytics, Harrsiburg, NC.

Background: Technology has allowed patients with Long-Term Conditions (LTCs) to access information through websites, portals, and Patient-centred organisations. 1) To understand, whether, retrospectively, there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education.

Methods: Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection. Fourteen (14) topic tags were applied over 1-month (March and April 2020) between 1) To understand, whether, retrospectively, there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education.

Results: 19 surveys completed from Health Professionals and 45 completed from community respondents (28 respondents at the time of reporting) and one directed to the community identified “Impact of renal disease and comorbidities on EV analysis” as key knowledge gaps.

Conclusions: In summary, the present survey identified key similarities and differences between current practices for the Urine Task Force and the urinary EV research community. Such information will be used to help guide future efforts to address key knowledge gaps.

A Potential Novel Variant of Slc4a4 Can Regulate the Functional Activity of the Electrogenic Na/HCO3 Cotransporter NBCe1-B

Seong-Ki Lee,1,2 Marie Michenkova,1 Michael F. Romero,1 Rossana Occhipinti,1 Bjarne G. Danielsen,1 Linda Eklund,1 Case Western Reserve University School of Medicine Department of Physiology and Biophysics, Cleveland, OH. 2Mayo Clinic Department of Physiology and Biomedical Engineering, Rochester, MN.

Background: The electrogenic Na/HCO3 cotransporter (NBCe1) regulates intracellular pH in many tissues and elicits vectorial HCO3− flow across many epithelia. Five variants of NBCe1 have been identified: Δα, mainly in kidneys; B, ubiquitous; -C, in brain; -D/E, in mouse reproductive organs. Because the A/D and B/C/E variants are transcribed from two distinct promoters, they have different NH2-termini (Nt). The Romero Lab developed an isoform-specific knockout (KO) mouse of NBCe1-A/D by causing a frameshifting mutation in the A/D variants’ unique Nt region (Chen et al, JASN 25:71A, 2014). Fang et al found that NBCe1-B (e1B) is expressed in kidneys of both WT and KO mice, and that e1B expression increases with metabolic acidosis in KOs (JAP Renal, 2018). They reached this conclusion by RT-PCR-amplification of B-variant– specific bands from KO kidneys. However, these amplifications generated several unidentified bands. Intrigued by these additional bands, we repeated the RT-PCR in an attempt to identify them.

Methods: Using TA cloning, we determined the sequences of two of the unidentified bands: (1) partial Slc4a4 product missing exon 4, which would lead to a frameshift, and (2) partial Slc4a4 product missing exons 4 & 5, but remaining in-frame. Five variants of NBCe1 have been identified: A, -mainly in kidneys; B, ubiquitous; Δα, in brain; -C, in brain; -D/E, in mouse reproductive organs. Because the A/D and B/C/E variants are transcribed from two distinct promoters, they have different NH2-termini (Nt). The Romero Lab developed an isoform-specific knockout (KO) mouse of NBCe1-A/D by causing a frameshifting mutation in the A/D variants’ unique Nt region (Chen et al, JASN 25:71A, 2014). Fang et al found that NBCe1-B (e1B) is expressed in kidneys of both WT and KO mice, and that e1B expression increases with metabolic acidosis in KOs (JAP Renal, 2018). They reached this conclusion by RT-PCR-amplification of B-variant– specific bands from KO kidneys. However, these amplifications generated several unidentified bands. Intrigued by these additional bands, we repeated the RT-PCR in an attempt to identify them.

Results: We found that neither mutant, alone, has activity even though Δα exon 4-5/e1B interacts with super-IRBIT. However, Δα 4-5/e1B has a dominant-negative (DN) effect on WT e1B. To test if these mutants are specific for KO mice, we inspected other WT tissues.

Conclusions: Contrary to our hypothesis, we found that e1B mutants (1) and (2) exist at least in kidneys, brain, and pancreas, leading us to conclude that cells could in principle regulate NBCe1-B activity by adjusting the amount of the novel DN variant Δα 4-5/e1B.

Funding: NIDDK Support, Other U.S. Government Support

A Survey of Current Trends in Urinary Extracellular Vesicle Research

Uta Erdbrügger,1 Elena S. Martens-Uzunova,1 Alicia Llorente,1 Luca Musante,1 Charles J. Blijdorp,2 Dylan Burger.2 1University of Virginia, Charlottesville, VA; 2Ontario Hospital, Ottawa, ON, Canada; 3Erasmus MC, Rotterdam, Netherlands; 4Oslo University of Medicine, Oslo, Norway.

Background: The Urine Task Force of the International Society of Extracellular Vesicles (ISEV) was created to advocate for best practices in this emerging area of research. The purpose of this survey was to present an overview of various aspects of a survey, conducted using SurveyMonkey by the Urine Task Force, to better understand current research practices in the study of urinary extracellular vesicles (eVes).

PO1073
**Methods:** We investigated the functional properties of SNVs in NBCe1 using immunocytochemical, biochemical, and electrophysiological assays. From NCBI data base, we identified 13 SNVs that have not previously been characterized in highly conserved, transmembrane domains of NBCe1-A.

**Results:** Immunocytochemical analysis revealed that I551F variant was present predominantly in the cytoplasm in HEK293 cells, whereas all other SNVs did not show obvious changes in subcellular distribution. Western blot in HEK293 cells demonstrated that the I551F variant showed impaired glycosylation and a 69% reduction in cell surface levels. To determine the role of Ile551 in more detail, we examined the significance of various mutant variants both in non-polarized HEK293 cells and polarized MDCK cells, which indicated that only I551F substitution resulted in cytoplastic retention. Moreover, functional analysis using Xenopus oocytes demonstrated that the I551F variant had a significantly reduced activity corresponding to 39% of that of wild-type variants, whereas any other SNVs and artificial I551 mutants did not show significant changes in activity. Finally, immunofluorescence study in HEK293 cells indicated that the I551F variant retains wild-type NBCe1-A in the cytoplasm.

**Conclusions:** These data demonstrate that I551F-NBCe1-A shows impaired transport activity predominantly through cytoplasmic retention, and suggest that the variant can have a dominant-negative effect by forming complexes with wild-type NBCe1-A.

**Funding:** Government Support - Non-U.S.

**PO1078**

**Diacidic Motif Is Required for Efficient Transport of NKCC2 to the Plasma Membrane**

Dalal Bakhos Al Douaihy,1,3 Elie Seayafan,2 Sylvie Demarzé,1,3 Kamel Laghmami,1,3 Martin Köhmf,7 Inserm, CNRS-ERL8228 Sorbonne Université, Paris, France; 3Philipps-Universität Marburg Fachbereich Medizin, Marburg, Germany; 4Centre de Recherche des Cordeliers, Paris, France.

**Background:** Mutations in the apical Na-K-2Cl cotransporter, NKCC2, cause type I Bartter syndrome (BS1), a life-threatening kidney disease. We have previously demonstrated that BS1 nonsense mutation V990X, which interacts with the highly conserved diacidic like motifs of NKCC2 C-terminus, compromises NKCC2 surface delivery through ER retention mechanisms. However, whether these diacidic like motifs are sufficient for anterograde trafficking of NKCC2 remained to be determined. Consequently, the aim of the present study was to investigate whether additional motifs are required for NKCC2 efficient transport to the plasma membrane.

**Methods:** NKCC2 protein expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 surface expression was monitored by cell surface biotinylation assay. NKCC2 stability and maturation was monitored by cycloheximide chase assay.

**Results:** Among the motifs identified as ER export signals in ion channels are the diacidic D/E-X-D/E motifs, which have been shown to promote interaction of cargo with the coat complex II (COP II) budding machinery. Interestingly, sequence analysis of NKCC2 C-terminus revealed the presence of two di-acidic motifs, I551F-EED and I551F-HAD, located upstream and downstream of BS1 mutation V998X, respectively. Importantly, mutation of I551F-EED to I551F-AAA disrupted glycosylation and cell surface expression of NKCC2, whereas mutation of I551F-HAD had no effect. Cycloheximde chase analysis demonstrated that the absence of the terminally glycosylated form of I551F-AAA was not due to increased rates of degradation of mutant co-transporters, but was instead caused by defect in maturation. Accordingly, co-immunolocalization experiments showed that I551F-AAA was trapped in the ER. Finally, overexpression of dominant negative mutants of Sar1 GTPase completely abolished NKCC2 maturation, clearly indicating that NKCC2 exit from the ER is COP II dependent.

**Conclusions:** Our data indicate that in addition to highly conserved diacidic like motifs, the diacidic D/E-X-D/E motif in NKCC2 C-terminus is a transport signal that controls NKCC2 transport from the ER and targeting to the cell surface. Elucidating the molecular mechanisms of the motif-facilitated ER export may help to develop therapeutic strategies targeting NKCC2 transport from the ER to the cell surface.

**Funding:** Government Support - Non-U.S.

**PO1079**

**Furosemide Alleviates Hypercalciuria and Hypomagnesaemia in Claudiun 16-Deficient Mice**

Natalia Biebling,1 Tilman Breiderhoff, Dominik Müller, Dyugu E. Yilmaz, Sebastian Bachmann, Kerin Mutig, Charite Universitätsmedizin Berlin, Berlin, Germany.

**Background:** Loss-of-function mutations in the CLDN16 gene encoding for claudin-16 lead to Familial Hypomagnesaemia with Hypercalciuria and Nephrolcalcinosis (FHHNC) in human. Claudin-16 resides in tight junctions of the thick ascending limb (TAL) and mediates paracellular reabsorption of divalent cations. The ensuing distal convoluted tubule (DCT), connecting tubule (CNT) and cortical collecting duct (CCD) perform transcellular Ca2+ and Mg2+ reabsorption via the transient receptor potential (TRP) channels, TRPV5 and TRPM6. DCT, CNT, and CCD exhibit unique functional and structural plasticity enabling them to compensate for defects of proximal salt reabsorption. To determine whether diuretic treatment may alleviate symptoms of Cldn16-deficiency due to compensatory stimulation of electrolyte reabsorption in DCT, CNT, and CCD.

**Funding:** Government Support - Non-U.S.

**PO1080**

**Cholesterol Efflux on Sodium-Sensitive Blood Pressure**

Karlin C. Oliveira,1,2 Robert L. Repetti,1,3 Rajeev Rohatgi,1,3 Stony Brook University Renaissance School of Medicine, Stony Brook, NY; 2Northport VA Medical Center, Northport, NY.

**Background:** Na sensitive BP is linked to greater mortality than Na resistant hypertension. Dyslipidemia and changes in plasma membrane (PM) lipid composition contribute to Na sensitivity. In addition, diets enriched in cholesterol (cholesterol) (1) raise cortical collecting duct (CCD) chol, (2) stimulate ENaC, and (3) repress natriuretic factors. Renal ABCA1, a cholest transport, increases in chol fed mice to mitigate cellular chool integration. Therefore, we hypothesize renal tubular ABCA1 ablation will lead to Na dependent changes in BP.

**Methods:** Transgenic mice (TGABCA1Rhoatgi) and WT control were housed in a 12h light/dark cycle and fed a standard diet (SM) (22 kcal% protein, 60 kcal% fat, 20 kcal% carbohydrate). The TG mice were treated with 1% cholesterol diet (FF) (27 kcal% protein, 70 kcal% fat, 13 kcal% carbohydrate). Enzyme-linked immunosorbent assay was used to measure cholesterol levels in serum and urine. Enzyme-linked immunosorbent assay was used to measure ABCA1 levels in kidney. Sodium sensitive BP was assessed by cell surface biotinylation assay. NKCC2 stability and maturation was monitored by cycloheximide chase assay. Western blot analysis in HEK293 cells predominantly in the cytoplasm in HEK293 cells, whereas all other SNVs and artificial I551 mutants did not show obvious changes in subcellular distribution.

**Results:** Immunoblotting of renal FF compared to WT kidney. FF vs FF mice post-dox feeding (Fig. 1; *, p<0.05 vs. FF post-dox). No difference in the ER exit from the ER is COP II dependent.

**Conclusions:** Tubular ABCA1 deficiency stimulates Na dependent SBP which we speculate is related to enhanced Na dependent ENaC and NKCC2 activity.

**Funding:** Veterans Affairs Support, Private Foundation Support
WNK4 is a Transducor of V2 Receptor Signaling in the Thick Ascending Limbs and Distal Convoluted Tubules

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Background: Vasopressin (AVP) is essential for water and Na+ homeostasis. In the kidney, its actions are mediated by the V2 receptor (V2R), which signals through protein kinase A (PKA). The phosphorylation of the Na+-Cl- cotransporter (NCC) and the Na+-K+-Cl- cotransporter 2 (NKKC2) by the WNK4-SPAK signaling pathway upregulates their activity and increases in response to AVP. WNK4 can be regulated by PKA through the phosphorylation of its RRS motifs in vitro models. Thus, we hypothesized that WNK4 mediates the activation of NCC and NKKC2 in response to AVP.

Methods: We transfected HEK293 cells with NKKC2 or the V2R with SPAK and either WNK3, WNK4, WT WNK4 or WNK4 with Ala instead of Ser in its 5 RRS motifs. Cells were stimulated with 30 nM forskolin or 1 nM desmopressin (DDAVP). We cross-bred our WNK4- strain (a C57BL/6 background) with 129sv mice while selecting for the full-length allele of NKKC2 to evaluate the phosphorylation status of NKKC2. DDAVP (5 nM) was administered in minioosmotic pumps for 3 days. Protein extracts were subjected to immunoblot. qRT-PCR of WNK4, Slc12a3 and 18S was carried out with Taqman probes. 12 h urine collections were conducted and water intake between the groups was equalized using gelled diets.

Results: In HEK293 cells, we found that an increase in phosphorylation of SPAK and of NKKC2 at T109 and T105 (SPAK regulated sites) with forskolin requires WT WNK4. In contrast, phosphorylation of Sl130 of NKKC2 was WNK4-independent. Only cells with WT WNK4 and the V2R showed an increase in SPAK phosphorylation when stimulated by DDAVP. DDAVP also increased WNK4's phosphorylation at S1196, SPAK- phosphorylation levels were also increased in total and phosphorylated WNK4, NCC, and NKKC2, as well as phosphorylated SPAK and Slc12a3 mRNA levels. These effects were absent in WNK4-4 animals. In contrast, WNK4- mice did respond to DDAVP by increasing AQP2 protein levels. In addition, WNK4- mice had increased water consumption at baseline and increased urine output when water-restricted, with a tendency towards lower total kidney osmolality.

Conclusions: Our data suggest that WNK4 is a transducor of AVP signaling in the TAL and DCT, modulating NKCC2 and NCC. This might contribute to the antidiuretic response and an increased urine output when water-restricted, with a tendency towards lower total kidney osmolality.

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Upregulation of NCC by Hypokalemia Involves Additional Mechanisms to Direct Cl- Sensing by WNK4

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Background: Cl-sensitive WNK4 kinase plays an important role in the modulation of NaCl reabsorption in the distal convoluted tubule (DCT). WNK4 activates the NaCl transporters, NCC and NKCC2, by activating the CaSR-WNK4-SPAK-NCC pathway in vivo. Models of CaSR-WNK1-mediating NCC inhibition during hyperkalemia. Our work shows that low K+ mediated upregulation of NCC does not result in an increase in WNK4 activity. We have previously shown that hypokalemia and low plasma [K+] increase in WNK4 protein levels and its phosphorylation at Ser64 and Ser1196 in WNK4-/- mice. In addition, WNK4 -/- mice had increased water consumption at baseline with Taqman probes. 12 h urine collections were conducted and water intake between the groups was equalized using gelled diets.

Methods: In WT mice, we observed increased activity of the WNK4-SPAK-NCC pathway in the kidney after exposure to 20% fructose or administration of dapagliflozin (p<0.001). Thiazide administration in the renal artery.

Results: In WT mice, we observed increased activity of the WNK4-SPAK-NCC pathway in the kidney after exposure to 20% fructose or administration of dapagliflozin (p<0.001). Thiazide administration in the renal artery.

Conclusions: Our data suggest that WNK4 is a transducor of AVP signaling in the TAL and DCT, modulating NKCC2 and NCC. This might contribute to the anti-diuretic response and an increased urine output when water-restricted, with a tendency towards lower total kidney osmolality.

Funding: Government Support - Non-U.S.
PO1086
High Dietary Potassium Increases Blood Pressure in a Rat Model of CKD
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Background: Potassium deficiency has been linked to increased incidence of cardiovascular disease (CVD). However, high dietary potassium (K+) intake is associated with lower blood pressure levels, and it has been shown that this regulation is intact in chronic kidney disease (CKD).

Methods: To address this, we induced CKD in rats that were fed a low KCl diet (0.03%), normal KCl diet (0.1%), modestly high KCl diet (0.8%), high KCl diet (2.5%) or high KCitrate diet (2.5%). The latter group was included to analyze if this response is intact in chronic kidney disease (CKD).

Results: Both the low and the high KCl diets increased blood pressure compared to the normal KCl diet, although the effect of the high KCl diets was more pronounced (Table). Higher dietary K intake caused higher plasma aldosterone levels, and high KCitrate further increased plasma aldosterone levels. nPCC was also increased in the high KCl diet compared to the low KCl diet. The effect of dietary KCl on nPCC, however, was lost with the high KCl diet. The high KCitrate diet attenuated the rise in blood pressure despite the highest plasma aldosterone and nPCC levels.

Conclusions: Although the inverse relationship between potassium and nPCC is intact in experimental CKD, high potassium diets cause hypertension possibly mediated by aldosterone. This rise in blood pressure is attenuated when potassium is given with citrate, despite high aldosterone and nPCC levels.

* P < 0.01 compared to normal KCl diet (ANOVA with post-hoc testing).
A.U., arbitrary units; BP, blood pressure; N.M., not measured.

PO1087
Rescuing Low Blood Pressure in Amiloride-Treated Mice by Low-Potassium Diet Relies on NCC Activation
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Background: NCC activity has been widely recognized to impact on blood pressure levels, as Gitelman syndrome, caused by inactivating mutations in the Slc12a3 gene, features arterial hypertension. In contrast, Familial Hyperkalemic Hypertension (FHHt) is a mendelian disease mainly driven by NCC overactivation. NCC activity is exquisitely regulated by changes in extracellular [K+], and it has been shown that this regulation might be at least in part responsible for the inverse relationship observed between dietary K+ consumption and blood pressure levels in animal models and in human populations. It has been shown that amiloride-induced hyperkalemia results in NCC inhibition, which can be prevented with administration of a low K+ diet. Thus, we decided to evaluate the role of NCC inhibition in the volume depletion and hypotension induced by amiloride treatment.

Methods: We treated 12-week-old C57Bl/6 male mice with amiloride at 25mg/K in the drinking water. During treatment, mice were kept on normal chow (0.4% NaCl, 0.8% K+) for 4 days, then switched to low K+ diet (0.1% K+), and at the 4th day of low K+ diet hydrochlorothiazide (HCTZ, 60 mg/kg/d, in the diet) treatment was started in a subset of mice.

Results: Amiloride-treated mice developed a PHA1-like syndrome (a severe hyperkalemic, salt losing nephropathy, with marked hypotension). Hyperkalemia and hypotension were prevented by low K+ diet. Basal blood pressure levels were re-established by day 4 on low K+ diet, while further treatment with HCTZ produced a steep increase in blood pressure of these animals. Immunoblot analysis of kidney lysates from amiloride-treated mice at various low K+ and repleted normal K+ levels were reversed by low K+ diet.

Conclusions: We show that the salt losing hyperkalemic phenotype induced by amiloride can be further mediated by low K+ diet and that this recovery is mediated by the increased activity of NCC.

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

PO1088
SALL3 Is a Salt-Responsive Distal Convoluted Tubule-Specific Transcription Factor Induced in Distal Neprhon Remodeling
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Background: We engineered constitutively active the SPK kinase (CA-SPPK) in the distal convoluted tubule (DCT), causing constitutive NCC activation, and DCT hypertrophy and hyperplasia. SPK expression was found to be repressed by sodium chloride cotransporter (NCC) (N, Slc12a3) in the DCT is parallel by an increase in DCT mass as an adaptive response to intravascular volume depletion or hypokalemia. The downstream regulatory factors that induce structural expansion of DCT are unknown.

Methods: Mice were engineered to constitutively active the SPK kinase (CA-SPPK) in the DCT, causing constitutive NCC activation, and DCT hypertrophy and hyperplasia. Gene expression analysis was performed in renal cortical tissue. Differential gene expression analysis was performed to compare 1) CA-SPPK vs wild type (WT-CT) on control diet and 2) CA-SPPK on high salt diet (CS-HS) and WT on high salt diet (WT-HS). Bioinformatic approaches were applied to identify the DCT-specific transcription factors (TFs) that are dependent on the NCC activation. TF protein localization and expression was evaluated by immunofluorescence and confocal microscopy, and image analysis tools.

Results: Differential expression analysis and cell deconvolution of the bulk RNA-seq using single-cell genome-wide RNA-seq bioinformatic analysis was performed in renal cortical tissue. Differential gene expression analysis was performed to compare 1) CA-SPPK vs wild type (WT-CT) on control diet and 2) CA-SPPK on high salt diet (CS-HS) and WT on high salt diet (WT-HS). Bioinformatic approaches were applied to identify the DCT-specific transcription factors (TFs) that are dependent on the NCC activation. TF protein localization and expression was evaluated by immunofluorescence and confocal microscopy, and image analysis tools.

Conclusions: In summary, Sall3 is the predominant DCT-specific TF that is activated during DCT expansion, suggesting that it is a key component of the core transcriptional regulatory circuit maintaining DCT cell identity as the DCT expands.

Funding: Private Foundation Support

PO1089
Chemogenetic Activation of the Distal Convoluted Tubule Enhances Sodium Excretion Through Rapid Dephosphorylation of the Sodium-Chloride Cotransporter
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Background: The distal convoluted tubule (DCT) plays a crucial role in the regulation of sodium and potassium balance, predominantly through its apical sodium chloride entry pathway, NCC, which is activated by N-terminal phosphorylation. This neprhin manages Gq-coupled GPCRs (GPCRs), including (proteinaseactivated F), ang2 (arginine vasopressin), and others. The role that these GPCRs play regulating DCT function has been a challenge to investigate as they are expressed within multiple cell types that alter kidney physiology. Design Receptors Exclusively Activated by Designer Drugs (DREADD) technology can be used to explore the physiological role of GPCR activation.

Methods: To explore the role of Gq-coupled GPCRs along the DCT, we bred DCT-specific inducible Cre Recombinase mice (NCC-creAKR) to Gq-coupled DREADD mice to create DCT-DREADD mice. We verified the localization of the Gq DREADD protein using immunohistochemistry. We then activated Gq signaling in DCT cells with i.p. injection of DREADD-specific agonist deschlorolarazocine (DCZ) and determined the abundance of phosphorylated NCC by Western blot. Lastly, we measured sodium excretion in metabolic cages for 4 hours following DCZ administration in WT compared to DCT-DREADD mice.

Results: We found that the Gq-DREADD protein was specifically expressed within the basolateral membrane of the DCT (Figure A). DCZ injection caused rapid dephosphorylation of NCC within 30 minutes to 15% of the abundance observed in DCT-

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1090
Mechanistic Importance of Reduced KLHL3 and CUL3 Expression in CUL3-A9-Mediated Familial Hyperkalemic Hypertension
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Background: Mutations in the ubiquitin ligase scaffold protein Cullin 3 (CUL3) cause the disease familial hyperkalemic hypertension (FHH). In the kidney, mutant CUL3 proteins localize with COP9 signalosome subunit JAB1 that negatively regulates CUL3 activity. This leads to CUL3-A9 autodegradation, and increased abundance of With-No-Lysine [K] Kinase 4 (WNK4), which inappropriately activates the downstream kinase SPAK, which then phosphorylates and hyperactivates the Na+-Cl- cotransporter (NCC). We showed lower that CUL3-alone does not increase WNK4, so the precise mechanism by which CUL3-A9 causes FHH is unclear. We hypothesized CUL3-A9 degrades Kelch-like 3 (KLHL3), the CUL3 substrate adaptor for WNK4; thus reduced abundance of KLHL3 combined with reduced CUL3 are mechanistically important in CUL3-A9-mediated FHH.

Methods: We studied Cal3 KO (Cul3+/−, mice, Cdl3 KO mice expressing CUL3-A9 (Cul3+/−Δ9), Cul3 heterozygotes expressing CUL3-A9 (Cul3+/−Δ9), compound Cul3 and Klhl3 heterozygotes (Cul3+/−Δ9, Klhl3+/−), and Jab1 KO (Jab1−/−) mice. All mouse lines were inducible and renal tubule-specific.

Results: CUL3-A9 did not promote degradation of CUL3 targets that accumulate in Cul3−/− kidney: WNK4, cykl, or NQO1 (a surrogate for the CUL3 substrate Nr2). In Cul3+/−Δ9 mice, CUL3-A9 prevented KLHL3 accumulation seen in Cul3−/− kidney and promoted KLHL3 degradation in Cul3+/−Δ9 mice. Higher NQO1 and lower cykl E abundances were observed in Cul3−/−Δ9 mice compared to control mice. Cul3−/−Δ9 mice displayed increased WNK4-SPAK activation and phospho-NCC abundance, and FHH-like phenotype with increased plasma [K+] and salt-sensitive blood pressure. Similarly, reduced CUL3 and KLHL3 abundances and increased abundances of WNK4 and phospho-NCC were observed in Jab1−/− mice.

Conclusions: Together, these data provide evidence for a mechanism of reduced KLHL3 and reduced CUL3 in CUL3-A9-mediated FHH. CUL3-A9 potently degrades KLHL3, but also exerts modest effects on other CUL3 targets, raising the possibility of undefined renal tubule phenotypes in human disease.

Funding: NIDDK Support, Private Foundation Support

PO1091
Non-Reabsorbable Anions Enhance Potassium Excretion by Multiple Mechanisms
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Background: Potassium (K+) secretion in the distal nephron (DN) is governed, in part, by the luminal-negative transepithelial potential (Vte), created by ENaC-mediated sodium reabsorption, and partially attenuated by paracellular chloride (Cl−) reabsorption. Part, by the lumen-negative transepithelial potential (Vte), created by ENaC-mediated sodium reabsorption, and partially attenuated by paracellular chloride (Cl−) reabsorption. Any intervention that reduces Vte increases K+ secretion.

Methods: To examine the effects of anions on K+ excretion, we performed perfusion experiments in the rat inner medulla on isolated DN segments. We exposed the DN segments to solutions containing 100 mmol/L KCl, 5% KHCO3, or 5% NaCl, which were isosmotic and isonitrogenous. KCl replaced NaCl in the solutions to investigate the effect of luminal Cl− on K+ secretion.

Results: When we replaced NaCl with KCl, K+ secretion increased by 5-fold compared to control. However, when we replaced NaCl with KHCO3, K+ secretion increased by 10-fold compared to control. When we replaced NaCl with NaCl, K+ secretion increased by 2-fold compared to control. These results suggest that luminal Cl− is a major determinant of K+ secretion.

Conclusions: These results suggest that luminal Cl− is a major determinant of K+ secretion.

Funding: NIDDK Support, Veterans Affairs Support

PO1093
Role of mTORC2/SKGl Signaling in Rapid Response to Acute K Load to Maintain K+ Homeostasis
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Background: The kinase mTORC2 phosphorylates SKG1 and is required for normal K+ secretion in the aldosterone-sensitive distal nephron. Aldosterone is known to play a role in mediating a sustained response through effects on SKG1 gene transcription, however, it is unknown how rapid responses are mediated. Here we have explored the role of mTORC2 and ENAC activity in the early response to an acute K+ load to regulate K+ secretion.

Methods: Inducible tubule-specific Rictor (a core component of mTORC2) knockout mice (TRKO) were generated (Pax8-rtTA/LC-1/Rictorflox/flox). Both WT and TRKO mice received control or 2% KCl via gavage following intraperitoneal vehicle or Bel-2 (an ENAC inhibitor) injection. Urea, K+, and Na+ in the urine was collected. ENAC and ROMK activity were measured in split open tubules by apical membrane patch clamp hz post gavage.

Results: Adult TRKO mice on normal diet displayed no abnormality except significantly elevated aldosterone. K+ administration by gavage triggered markedly greater net Na+ and lower K+ excretion in TRKO than WT mice, with differences detectable within 1 h of gavage. Benzamil induced a greater netureas in WT than in TRKO mice, and more strongly suppressed kaliuresis, consistent with greater ENAC activation in WT than in TRKO. The response of WT occurred rapidly, before significant change in aldosterone. In benzamil-treated mice, the kaliuresis and kaliuresis of WT and TRKO mice were comparable, strongly supporting the idea that KC1 induced
ENaC-dependent K+ secretion in WT, and that this response is defective in TRKO. Patch clamp analysis revealed decreased ENaC activity in WT but not in TRKO mice, and no change in ROMK activity in WT or TRKO by KCi1 gavage. Membrane expression of cleaved α- and γENaC were significantly increased in WT but not in TRKO mice receiving KCi1 gavage. No significant increase in membrane expression of ROMK was observed in WT or TRKO gavage. Finally, both SGK1 and Nedd2-2 phosphorylation were increased in WT but not TRKO mice receiving KCi1 gavage.

Conclusions: Overall, the data strongly suggest that an acute K+ load acts through mTORC2/SGLK1 to rapidly stimulate ENaC but not ROMK to promote K+ secretion. These effects are primarily due to local renal tubular K+ sensing.

Funding: NIDDK Support, Private Foundation Support

PO1094
Structural Determinants of mTORC2 Substrate Specificity and SGGK1 Phosphorylation Revealed by Cryogenic Electron Microscopy
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Background: mTORC2 is a multi-subunit kinase complex central to multiple essential signaling pathways. Notably, it responds to hormonal signals and local electrolyte concentrations to phosphorylate SGGK1 and regulate K+ secretion in the renal tubules. Two core subunits, Rictor and mSin1 distinguish mTORC2 from its much better characterized relative, mTORC1. Two other subunits, mTOR itself and a small scaffold, mLST8, complete the core complex. Previous mTORC2 reconstructions have lacked key regions of the >1 MDa complex, particularly determinants of specificity.

Methods: Core mTORC2 subunits were expressed in Exp293F cells and purified using new methods for on grid purification. cryo-EM was performed using Krios at SLAC for high energy electrons for density maps of human mTORC2. Structures were solved for apo-complex at overall 3.23 Å resolution, and for co-complexes with substrates, SGGK1 and its γγγ subunit, and 18 and 3.44 Å, respectively.

Results: The apo-complex reveals architectural features of functionally important domains, including specific side chain positions and interactions, which are visualized for the first time. In particular Rictor/Ser-1624 and Ser-1625 were observed to engage phosphorylation Revealed by Cryogenic Electron Microscopy, and explains mTORC2 resistance to the effects of this clinically important mTORC1 inhibitor. In addition, mSin1, the other defining subunit of mTORC2, is seen to form extensive contacts with Rictor, including an extended strand, which makes multiple weak contacts with a Rictor helical cluster. Most notably for the first time, mLST8 plays a central role in the interplay between the core-complex with mLST8—but not the Akt co-complex, we saw a marked change in the conformation of the mLST8 N-terminal extended strand in a manner consistent with previous functional data identifying this region as required for phosphorylation of SGGK1, but not Akt, thus providing a structural basis for differential regulation.

Conclusions: These findings provide new structural insight into mTORC2 specificity and context-dependent activities, and foundation for further mechanistic studies. Further, these findings provide a potential avenue toward highly selective mTOR modulators with potential clinical utility.

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PO1095
In Vivo Influence of a Protease-Resistant Epithelial Sodium Channel Gamma Subunit on Fluid Homeostasis

Background: Extracellular fluid depletion promotes proteolytic processing of ENaC's γ subunit. Removal of the subunit's inhibitory tract enhances channel open probability. Although several cleavage sites exist distal to the γ subunit's inhibitory tract, only one known site resides proximal to the inhibitory tract: a furin cleavage site (RRKK)12. We hypothesized that a mouse expressing a protease-resistant ENaC γ subunit would exhibit signals from A- and B-types of ICs. However, it is not possible to specifically change the driving force for Cl− at luminal or basolateral sides, which is used for transepithelial studies to identify Cl− types of certain cells on periphery. The technique of split-opening isolated CD allows unambiguous monitoring of alterations in function in multiple individual cells within the split-opened area. However, acid-secreting A- and base secreting B-type of ICs cannot be easily separated in functional studies despite virtually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether B-type of ICs cannot be easily separated in functional studies despite virtually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether local renal tubular K+ sensing. These effects are primarily due to local renal tubular K+ sensing.

Funding: NIDDK Support, Private Foundation Support

PO1096
A Rare Case of Acquired 11-Beta-Hydroxysteroid Dehydrogenase Deficiency
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Introduction: 11-Beta Hydroxysteroid Dehydrogenase (HSD11B) is an enzyme that is involved in steroid hormone physiology. HSD11B enzyme exists in two isoforms, HSD11B-type 1 and type 2. Type 2 isomer is responsible for converting cortisol to inactive cortisone. Plasma concentration of cortisol is approximately 100-fold higher than aldosterone and activation of mineralocorticoid receptors by cortisol is normally limited due to its conversion to inactive cortisone at the sites of aldosterone action by the enzyme HSD11B-type 2. We are presenting a rare case of HSD11B deficiency in a patient taking herbal supplementation.

Case Description: A 73-year-old female with PMH of hypertension, hyperlipidemia and chronic pain was admitted to the hospital with fatigue and shortness of breath. She denied any history of diarrhea or recent use of diuretics or laxatives. She has a history of using some herbal supplements in large quantities for pain control. Initial blood pressure was 140/80 mmHg. EKG showed sinus bradycardia with PVCs and bigeminy. The lab results are summarized in table A. She received aggressive potassium supplementation and spironolactone with subsequent improvement of her condition.

Discussion: HSD11B deficiency is either congenital or acquired by ingestion of licensed or its derivatives (glycinebicyclic and glycinebicyclic acids). The deficiency results in a decreased conversion to cortisone and accumulation of cortisol. The effect of cortisol on the mineralocorticoid receptor results in hypokalemia, metabolic alkalosis, and low aldosterone and renin activity. The diagnosis requires careful history and identification of specific clinical features and biochemical abnormalities.

PO1097
New Method to Discriminate Function of A- and B Type of Intercalated Cells in Split-Opened Collecting Ducts
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Background: The collecting duct (CD) is a highly adaptive terminal part of the nephron and is essential for fluid and electrolyte homeostasis. Electrically uncoupled principal and intercalated cells (PCs and ICs) perform different physiological tasks and exhibit rather distinctive morphology. However, acid-secreting A- and base secreting B-type of ICs cannot be easily separated in functional studies despite virtually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether local renal tubular K+ sensing. These effects are primarily due to local renal tubular K+ sensing.

Methods: We used BCEF/C-sensitive intracellular pH (pH) measurements in split-opened CDs followed by immunofluorescent (IF) detection of AQP2 and pendrin from the collecting duct (CD) is a highly adaptive terminal part of the nephron and is essential for fluid and electrolyte homeostasis. Electrically uncoupled principal and intercalated cells (PCs and ICs) perform different physiological tasks and exhibit rather distinctive morphology. However, acid-secreting A- and base secreting B-type of ICs cannot be easily separated in functional studies despite virtually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether local renal tubular K+ sensing. These effects are primarily due to local renal tubular K+ sensing.

Results: Expression of the prostate specific antigen in oocytes, along with ENaC (N = 15), increased amiloride-sensitive currents, compared to oocytes with ENaC but no prostatic (N = 15; p < 0.0001). In oocytes expressing a Q4 gamma subunit (N = 15), prostatic no longer. Western blot of PgLase-digested tissue lysates revealed a full-length (60 kDa) γ subunit and two shorter proteins, consistent with subunits either cleaved at the furin site (~53 kDa) or at a more distal site. Tissues from Q4 mice lacked the 53 kDa band, suggesting impaired Furin site cleavage. Blood K+ was normal in Q4 mice (N ≥ 7 for each sex and genotype). On a LSD, Q4 male mice exhibited greater loss of body fluid in response to dietary Na depletion. Females did not show a impaired body fluid retention, suggesting additional compensatory mechanisms.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: We show that CIC-K2/C1-channel is exclusively expressed on the basolateral side of C2 cells in 3D cultures. However, it is likely that CIC-K2/C1-dependent H+/HCO₃⁻ transport. Indeed, CIC-K2 blocker, NPPB, had no effect on pHi in PCs, whereas it caused acidification or alkalization in different subpopulations of ICs in WT but not CIC-K2-/-. If assay of the same CDs revealed that NPPB decreased pHi in pendrin-positive B-type of ICs. Induction of metabolic acidosis markedly increased A/B cell ratio from 74% to 145%. Furthermore, dietary acidification also resulted in significantly increased H⁺ secretion (assessed as recovery after acidification) in A-type and decreased pH transport in B-type of ICs.

Discussion: Despite being extremely rare, metabolic acidosis induced by drug interactions such as between Paracetamol and Fluoxacinil is a severe and potentially life-threatening disorder. We recognize the relevance of this case since these drugs are commonly prescribed together.

PO1100
Dietary Ammonium Exacerbates Pyelonephritis in Mice Prone to Vesicoureteral Reflux
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Background: In a mouse model of urinary tract infection with Uropathogenic E. Coli (UPEC-UTI) dietary NH₄Cl (AC) induces metabolic acidosis and increases UPEC burden in reflux prone C3H-HeN but not Trit4 deficient, C3H-HeJ mice. We have confirmed and extended these studies by comparing the inflammatory response in C3H-HeN mice fed AC-diet vs. standard chow (SC), and by examining the effect of HC1-acidosis.

Methods: Female C3H-HeN mice were fed: standard chow (SC), NH₄Cl (2% w/w; AC), or 1g/ml 0.4 N HCl supplemented chow (HC-1). Acid-base state was assessed by blood /gas analysis using an iSTAT ® G3+ and urine pH. UPEC burden (cfu/g) was determined by quantitative culture. Statistics: Two-tailed T-test or Mann-Whitney U Test p<0.05.

Results: Consistent with higher UPEC burden in blander and kidney and increased chemokine/cytokine production, Ly6G⁻ kidney neutrophil infiltration, phagocytosis of UPEC-GFP (GFP mean fluorescence intensity, MFI, in Ly6G⁻ neutrophils) and oxidative burst (DHR123 fluorescence, MFI) were quantitated by flow cytometry. Statistics: Two-tailed T-test or Mann-Whitney U Test p<0.05. Ammonium exerts its effect on both UPEC burden and inflammatory response.

Conclusions: Dietary ammonium chloride impairs clearance of UPEC-UTI and exacerbates pyelonephritis. The effect of dietary ammonium is unrelated to acidosis and neutrophil function.

Funding: Private Foundation Support

PO1098
Piezo 1 in Intercalated Cells (ICs) Mediates Flow-Induced [Ca2+]i Transients in Mouse Cortical Collecting Duct (CCD)
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Background: Within the CCD, an acute increase in tubular fluid flow rate (TFFR) exposes principal cells (PCs) and ICs therein to hydrodynamic forces. In response, a biphasic increase in [Ca²⁺]i is observed, with an immediate high amplitude increase due to release of IP3-sensitive internal Ca²⁺ stores coupled to extracellular Ca²⁺ entry at the basolateral membrane. This is followed by a decrease to a plateau that is higher than baseline and sustained by luminal Ca²⁺ entry (Liu et al., 2003; 2005; 2007). This increase in [Ca²⁺]i is necessary for BK channel-mediated flow induced K⁺ secretion (FIKS) in the microperfused mammalian CCD. We have recently reported that PIEZO1, a mechanosensitive, Ca²⁺ permeable channel, is expressed on the basolateral membranes of PCs and ICs in the mouse CCD (Dalghi et al., 2019).

Methods: To examine whether IC Piezo 1 expression contributes to the increase in [Ca²⁺]i triggered by TFFR, we generated a mouse with targeted deletion of Piezo 1 in ICs (IC-Piezo1-KO).

Results: Immunofluorescence analyses of kidneys harvested from mice (C57BL/6) expressing PIEZO1-tdTomato revealed a significant increase of PIEZO1 expression in ICs from mice fed a high K (HK, 5% K, n=4) vs. standard K (SK, 1% K, n=4) diet for 10 days. Fluorescence intensity ratios (FIRs; ratio of the Ca²⁺ i in ICs (p≤0.001). However, ICs from HK-fed IC-Piezo1-KO mice exhibited a reduced or absent increase in [Ca²⁺]i in response to Yodalan vs. SK-fed control mice (p=0.001). Indeed, from HK-fed IC-Piezo1-KO mice exhibited a reduced or absent increase in [Ca²⁺]i in response to Yodalan vs. SK-fed control mice (p=0.001).

Conclusions: We find that Piezo is upregulated in the CCD by a HK diet and contributes to the TFFR-induced increase in [Ca²⁺]i in ICs necessary for FIKS.

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PO1099
An Extremely Rare Interaction Between Two Commonly Used Drugs
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Introduction: The use of Paracetamol and Fluoxacinil can result in an elevated anion gap metabolic acidosis. Interaction between these drugs is a rare disorder that results from accumulation of pyroglutamic acid. Affected patients are usually women with chronic illness, sepsis, and malnutrition.

Methods: We present the case of a 79 year-old hypertensive and diabetic woman who had been treated with Paracetamol and Fluoxacinil in high doses as the leading cause of elevated anion gap metabolic acidosis. Despite these drugs were immediately stopped and sodium bicarbonate was started, the patient showed no clinical improvement and presented with respiratory failure. Hemodialysis was started to correct the acid-base disorder.

Discussion: Despite being extremely rare, metabolic acidosis induced by drug interactions such as between Paracetamol and Fluoxacinil is a severe and potentially life-threatening disorder. We recognize the relevance of this case since these drugs are commonly prescribed together.

PO1101
Molecular Insights into the Structural and Dynamical Changes of Calcium Channel TRPV6 Induced by Its Interaction with Phosphatidylinositol-4,5-Biphosphate
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Background: Transient receptor potential vanilloid subfamily member 6 (TRPV6) is a Ca²⁺-selective channel that mediates Ca²⁺ entry into epithelial cells as the first step of the transcellular Ca²⁺-transport pathway. TRPV6 is expressed in the kidney, intestine, and other epithelial tissues, and the dysregulation of this channel has been implicated in cancers. TRPV6 and its close homologue TRPV5 are activated by phosphatidylinositol (PtdIns(4,5)P₂) and other phospholipids, and the dysregulation of this channel has been implicated in cancers. TRPV6 and its close homologue TRPV5 are activated by phosphatidylinositol-4,5-biphosphate (PIP₂); however, it is less clear how PIP, activates TRPV6 at the molecular level.

Methods: Recently, a structure of rabbit TRPV5 complex with dioctanoyl (diC8) PIP₂, a soluble form of PIP₂, was determined by cryo-electron microscopy. Based on this structure, the concept of human PIP₅Kα (a Ca²⁺ channel activator) is consistent with the structural data that residues R302 and K484 in TRPV5 are responsible for the binding of diC8 PIP₂. The binding of PIP₂ is expected to induce conformational changes in TRPV5, which is consistent with the structural data that residues R302 and K484 in TRPV5 are responsible for the binding of diC8 PIP₂. The binding of PIP₂ to TRPV6 increases the distance between the diagonally opposed residues D542 and E546 in the selectivity filter as well as the distance between the diagonally opposed residues M578 and D542 in the selectivity filter. Secondary structure and density analyses show that residue M578 in TRPV6 in the presence of PIP₂, a soluble form of PIP₂, was determined by cryo-electron microscopy. Based on this structure, the concept of human PIP₅Kα (a Ca²⁺ channel activator) is consistent with the structural data that residues R302 and K484 in TRPV5 are responsible for the binding of diC8 PIP₂. The binding of PIP₂ is expected to induce conformational changes in TRPV5, which is consistent with the structural data that residues R302 and K484 in TRPV5 are responsible for the binding of diC8 PIP₂.
Conclusions: Simulation results indicate that PIP, increases the fluctuation of the key residues in both the selectivity filter and the lower gate of TRPV6. In addition, PIP reduces the helix occupancy of a key residue in the lower gate. Furthermore, the diameters of both the selectivity filter and the lower gate are increased by PIP. These changes likely contribute to the opening of the TRPV6 channel.

Funding: NIDDK Support

PO1102
Lithium Treatment Induces Changes in E-Cadherin, β-Catenin, and Na+/K+-ATPase β1 in Rat Inner Medullary Collecting Duct in a Time-Dependent Manner

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Background: Lithium (Li)-induced Nephrogenic Diabetes Insipidus (NDI) develops in around 40% of psychiatric patients receiving Li treatment. NDI is characterized by the inability of the kidney to concentrate urine due to insufficient water reabsorption in the kidney collecting duct (CD). Studies in rats have shown that Li induces a cellular compositional change of the CD with a fractional decrease in the ratio of principal-to-intercalated cells after 4 weeks of Li. This cellular remodeling is reversible in rats undergoing recovery for 19 days following 4 weeks of Li treatment. We aimed to investigate if regulation of the cell-contacts E-cadherin and β-catenin have a role in the cellular remodeling. The Na’/K’-ATPase was also investigated due to previously shown influences on cell polarity and cell-contact formation in kidney cells (Rajasekaran et al. Mol Biol Cell).

Methods: Immunohistochemistry (IHC) was performed on rat kidney sections used in previously published studies (Christensen et al, JPP, 2006; Treppiccione et al, JPP, 2011). Sections from rats treated with Li for 4, 10 and 15 days and 4 weeks were stained using antibodies against the cytoplasmatic domain of E-cadherin, β-catenin and Na’/K’-ATPase β1-subunit. Sections from rats that had undergone recovery for 6 and 12 days following 4 weeks of Li treatment were stained for β-catenin.

Results: E-cadherin and β-catenin labeled basal and lateral plasma membrane domains in the inner medullary CD (IMCD). In the proximal part of IMCD, the labeling was absent from the basal plasma membrane domains of multiple cells after 4 and 10 days of Li treatment and was present again after 4 weeks of Li. In addition, the basal labeling of E-cadherin was absent from some cells after 12 days of recovery. IHC of the Na’/K’-ATPase β1-subunit revealed a similar subcellular localization, and the protein was not present in the basal plasma membrane domains of multiple cells in the proximal part of the IMCD already after 4 days of Li.

Conclusions: The subcellular localization of the adhesions junction proteins E-cadherin, β-catenin and Na’, K’-ATPase β1 is affected by Li treatment in the proximal part of the IMCD. In addition, the absence of labeling from the basal plasma membrane domains appears to occur prior to the cellular remodeling.

Funding: Private Foundation Support

PO1103
Deletion of the EP3 Receptor in the Kidney Tubule of Adult Mice Has No Impact on the Major Channels and Transporters Involved in Kidney Water Handling

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Background: Prostaglandin E2 (PGE2) is an important lipid mediator modulating various aspects of kidney function. PGE2 exerts its effects via four PGE2 receptors, EP1, EP4, but it is unclear which PGE2 effects are mediated through which receptor. The EP3 receptor is expressed in the thick ascending limb (TAL) and the collecting duct, where it is proposed to inhibit CAMP generation and NaCl and water reabsorption. However, EP3 is also expressed in endothelial cells of arteries and arterioles, that also play a role in kidney function.

Methods: To assess the tubular role of EP3 in adult mice we generated a mouse model based on the Pax8Cre system with doxycycline-dependent deletion of EP3 along the renal tubule and assessed their renal phenotype in respect to water handling. qPCR and RNAscope confirmed that EP3 was highly expressed in cortical and medullary TAL and connecting tubules, but it was not detected in proximal tubule and thin limbs. In addition, the expression of AQP1, AQP4, AQP11, Iba1 (microglial marker), Lamp2 (pro-autophagic factor), Bax (pro-apoptotic factor).

Results: Two weeks after treatment with doxycycline, EP3 mRNA expression was 365

PO1104
Bayesian Identification of Transcription Factors that Regulate Aqp2 Gene Expression

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Background: Renal collecting duct and connecting tubule cells selectively express the water channel aquaporin-2 (AQP2) and Aqp2 gene transcription is strongly regulated by vasopressin (V2 receptor). However, the precise transcription factors (TFs) responsible for regulation of expression of AQP2 remain largely unknown. Here, we used Bayesian data integration techniques to identify these TFs.

Methods: The general strategy is to use Bayes’ Rule to integrate several -omic datasets into a curated list of 1344 TFs present in the mouse genome with regard to probability of regulating Aqp2 gene transcription. To prioritize TFs, existing proteomic and transcriptomic data, ATAC-Seq, histone H3K27-acylation ChIP-Seq, and RNA-polymerase II ChIP-Seq data are used. Beyond this, we use additional -omic datasets to prioritize TFs that are regulated by vasopressin. Finally, we carried out new RNA-Seq experiments mapping the time course of vasopressin induced changes in the transcriptome of mouse mpkCCD cells to further prioritize TFs that change in tandem with AQP2.

Results: The analysis identified 17 TFs out of 1344 in the mouse genome that are most likely to be involved in regulation of Aqp2 gene transcription. These TFs included eight that have been proposed in prior studies to play a role in Aqp2 regulation, viz. Cebpb, E2f1, E2f3, Ets1, Jun, Jnk, Nr4a1, and Sp1. The remaining nine represent new candidates for future studies (Aif1, Irf3, Klf5, Klf6, Mef2d, Nfly, Nr2f6, Stat3, Nr4a1).

Conclusions: The Bayesian analysis has identified the TFs most likely to bind to Aqp2 cis-regulatory elements and likely to be regulated by vasopressin stimulation, providing a roadmap for future studies to understand regulation of Aqp2 gene expression.

Funding: Other NIH Support - Division of Intramural Research, National Heart, Lung, and Blood Institute (project ZIA-HL001285 and ZIA-HL006129, M.A.K.)

PO1105
The Enhanced Expression of AQP4 in Cerebral Ischemia Is Attenuated in AqP11 Heterologous Knockout Mice

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Background: The role of aquaporins (AQP’s) in the brain edema needs to be clarified to advance its treatment. Since the importance of AQP4 for the formation of brain edema has been shown, expression of AQP11, expressed in the brain capillary, may also be important for the regulation of brain edema. In fact, we recently reported the associated expression of AQP4 and AQP11 in osmotically challenged AQP11 heterologous knockout mice (HKM) (Koike S et al. Biochimie. 2021).

Methods: Both common cervical arteries were ligated for 15 min or 60 min to produce an ischemic-reperfusion model of brain infarction. On one or two days after the reperfusion, total RNA in the brain between Bregma and Lambda was isolated from wild mice and HKM. A real-time RT-qPCR was employed to examine the expression levels of several genes including AQP1, AQP4, AQP11, Iba1 (microglial marker), GFAF (astrocyte marker), Lamp2 (pro-autophagic factor), Bax (pro-apoptotic factor).

Results: Gene expression profiles were similar between wild mice and HKM in Iba1 (increase), Lamp2 (increase) with more severity in 60 min ligation and in the second day. A similar profile was also observed with slightly decreased AQP1 by 5-22%. In contrast, the expression profiles of AQP4 and GFAF were outstanding in that both were more highly induced in wild mice than HKM, by 56% vs. 21% and by 750% vs. 335%, respectively, with further increases in 60 min ligation and in the second day. The results suggested the activation of astrocytes expressing AQP4 by the reperfusion, which might be attenuated in HKM. In agreement with this, the expression of Bax was increased in wild mice by 18% with 60-min ligation while it was decreased by 12% in HKM, suggesting a smaller brain damage in HKM. Interestingly, AQP11 expression was decreased after reperfusion by 13-25% in wild mice while it was decreased in HKM in 25-30%. The results suggest that this further AQP11 decrease in HKM may have attenuated the increasing AQP4 expression after reperfusion.

Conclusions: The increased AQP11 expression in HKM attenuated the enhanced expression of AQP4 and Bax in a mouse ischemia-reperfusion model. Thus, the inhibition of AQP11 may alleviate the brain edema by attenuating the expression of detrimental AQP4 in brain infarction.

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PO1106
Acute Hemoglobin Level Drop Based on Body Volume Gained

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Background: Hemoglobin (Hb) changes with blood transfusions have been widely studied, but to our knowledge, Hb drop associated with volume gain have not been studied. High fluid volume infusion in critically ill patients always result in Hb drop, but the exact extent of Hb change associated with fluid gain has not been studied. We aimed to assess Hb changes based on daily volume gained among anuric hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: Chronic anuric hemodialysis (HD) patients without active bleed admitted to our institution for reasons other than dialysis were included. Strict input/output measurements and Hb levels peri-HD were obtained. Post-HD levels were measured at least 12 h post treatment to allow for equilibrated fluid compartmentalization. Changes in Hb per L of body volume gained were calculated.

Five HD individuals were included. Average age 60±7.2 years, 6 males, 4 females, estimated fat free mass (FFM) 49±3.5 Kg, pre-HD Hb 9.74±1.28, post-HD Hb 9.36±1.28 g/dL, positive fluid balance per patient 1187±775 mL. Average Hb drop was -0.19±0.38 g/dL per L of fluid gained, or 0.004±0.12 g/L/L of fluid gained/ Kg of body weight.

Conclusions: Hemoglobin drop with large fluid infusion may be studied in the anuric HD population. Our pilot study indicates thus far that Hb drop may be ~0.2 g/dL/L on an average or a maximum of ~0.8 g/dL per liter of positive fluid balance. Additional data are being collected. Our study may help clinicians gauge for possible blood loss during large fluid infusion required for hemodynamically unstable patients.

PO1107
A Salty Goodbye to Diuretic Resistance: Hypertonic Saline
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Introduction: Understanding the complex interplay of Cardiorenal physiology and pathophysiology in diuretic resistance requires a deep understanding of RAAS, ADH, and virtually all segments of the nephron. To treat, requires not only understanding but also the ability to investigate and differentiate. However, a treatment that can inhibit RAAS (directly and indirectly), stimulate Cardiac Output, improve GFR, and increase natriuresis could be vital. The potential causes of diuretic resistance arise from the RAAS system and the individual nephron segments. The RAAS system however is the most universal target (when inhibited). While DCT, ASDN, CD and CCT are involved, regardless of which segment is primary, targeting the RAAS system would likely have significant benefits in all diuretic resistance. 3% Saline has the ability to improve Cardiac Output and decrease SVR, increase diuresis, inhibit RAAS (directly and indirectly), and stimulate ANP. Therefore, the answer to Diuretic Resistance is 3% Saline.

Case Description: A 55 y.o. AAF presented to the hospital for severe edema and shortness of breath. PMHx of HFpEF, DM, IHTN, CKD stage 5 (non-nephrotic). She presented with AKI III, severe hyponatremia, and anasarca. Echo revealed EF 40%, biatrial enlargement, RV overload and reduced RV function. She was initially treated with high dose furosemide but did not improve. She was given Metolazone which caused worsening hyponatremia which was treated with 100mL of 3% Saline. This caused an immediate increase in urine output and sodium. She was then changed to a bumex drip and high dose spironolactone (200mg) with some improvement (via objective urine electrolyte assessment) she was still inadequately diuresed. She was then treated with 3% + Loop pulse dosing and sustained a robust diuresis of ~3L of urine and maintained urinary sodium >50.

Discussion: The potential causes of diuretic resistance arise from the RAAS system and the individual nephron segments. The RAAS system however is the most universal target (when inhibited). While DCT, ASDN, CD and CCT are involved, regardless of which segment is primary, targeting the RAAS system would likely have significant benefits in all diuretic resistance. 3% Saline works as a potent IVF to improve Cardiac Output, decrease SVR, improve renal blood flow, inhibit RAAS, inhibit ADH, and stimulate ANP. Using 100mL of 3% saline to augment diuresis (or alone) causes improvement in virtually all Cardiorenal parameters. The NaCl load directly inhibiting RAAS through distal NaCl delivery (salt load also increases salt wasting), this causes decreased arterial arteriolar constriction and thus further improving GFR. It also stimulates ANP in the RA to inhibit RAAS and ADH indirectly.

PO1108
Enhanced Diuresis with Sequential Nephron Blockade
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Introduction: Achieving volume control in patients with severe edema can be challenging, as diuretic resistance may occur. In such cases, sequential nephron blockade (SNB), a less invasive diuretic use strategy should be considered.

Case Description: A 60-year-old woman with HIV and Dilated Cardiomyopathy s/p CRT-D presented with dyspnea and anasarca despite conservative and losartan. In the ED she weighed 370 Lbs., had stable hemodynamic parameters, hypoxemia, diffuse lung infiltrates and low CD4 count. Oxygen, IV loop diuretics and Bactrim were initiated for concerns of PCP and HF. Despite an average UO of 3 L/day she had no meaningful weight loss, protracted lung congestion, hyponatremia and developed radiocontrast nephropathy after CTA. Fluid restriction and SNB with IV furosemide and loop agents were instituted. Tolvaptan was added to perform maximal diuresis of ~8-11 L/day, restored normonatremia and was hemodynamically and metabolically well tolerated. Within 12 days, weight loss of 154 Lbs. was achieved with major clinical improvement.

Discussion: Loop agents are a mainstay for diuresis in patients with volume overload, diuretic resistance can occur through various mechanisms, including the hypertrophy of the distal nephron and loss of function due to AKI. SNB provides a unique approach by strategically targeting ultrafiltrate dynamics in a stepwise manner and interfering with fluid reabsorption within various tubular segments. Central to this principle, the ability to maximize drug bioavailability and parenteral administration is initially necessary. Close hemodynamic and metabolic surveillance are mandatory as the mobilization of vast amounts of extracellular fluid may result in significant complications. Remarkably, in this case, while her eGFR was 25% she achieved 11 L diuresis (30% of UF) safely. This underscores the enormous capacity for fluid sequestration in the extracellular space and the crucial role of trans-compartmental fluid shifts in HF. SNB has been available for years and various diuretics combinations are plausible. This case exemplifies the effectiveness of a novel regimen with vaptans in promoting voluminous diuresis and aquaresis, improving outcomes and decreasing length of stay.

PO1109
Functional Sodium Magnetic Resonance Imaging of Human Kidney

Background: Maintenance of a cortico-medullary concentration gradient (CMG) is required for urine concentration. We explored the ability of 23NaMRI in measuring 1) the dynamics of CMG for the first time compared to urinary osmolality after a water load and 2) the CMG in kidney disease.

Methods: We conducted an exploratory pilot study for 10 healthy controls following water load then 5 cardiacorenal patients with kidney disease. 1) Fasting healthy controls provided urine samples to measure osmolality and baseline 23NaMRI scans were performed. They were instructed to ingest water (15 mL/kg) within 15 minutes. Four subsequent sodium images and urine samples were acquired at 15 min intervals starting one hour after water ingestion. 2) Cardiorenal patients underwent an MRI scan, provided a blood and urine sample, but no water loading.

Results: Mean age of the 10 healthy controls was 41.8 ± 15.3 years. In the morning fasting, medulla/cortex ratio was 1.55 ± 0.11 with concurrent urinary osmolality measured at 814 ± 121 mOsm/L. Mean a SD fasting urinary osmolality dropped significantly to 73 ± 14 mOsm/L, p=0.001. Mean medulla/cortex ratio dropped significantly to 1.31 ± 0.09 mOsm/L for maximal dilution, p=0.002. Figure 1 displays changes of 23NaMRI pictures before (A) then 1h (B), 1h15 (C), 1h30 (D) and 1h45 (E) after a water load. Urinary osmolality and medulla/cortex ratio are significantly correlated, r=0.54, p=0.0001. Mean age of the 5 cardiacorenal patients was 76.6 ± 12.2 years, eGFR was 54 ± 37 mL/min/1.73m2. Urinary osmolality was 498 ± 145 mOsm/L and medulla/cortex ratio was 1.35 ± 0.11. We measured corticomedullary osmolality and showed in cardiacorenal patient with different level of eGFR to show the ability and feasibility to measure this gradient in pathological settings.

Conclusions: We explored CMG dynamically every 15 min in healthy controls and demonstrated significant changes after a water load. We were also able to acquire 23NaMRI pictures in cardirenal patients with kidney disease with plans for future analyses.

PO1110
Validity of a Simple Equation to Estimate Urine Output in Outpatients with Suspected Nephrolithiasis
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Background: We previously developed and validated an equation to estimate urine volume from spot urine creatinine, demographic variables, and body weight in patients with or without nephrolithiasis. We hypothesized this equation could accurately estimate daily urine output in outpatients with nephrolithiasis.

Methods: Among persons submitting specimens to Litholink Laboratories between May 2013 and January 2016, we identified 19,884 individuals who had two 24 hour urine collections on consecutive days, with creatinine excretion rates ±10%. We used Pearson correlations and Bland-Altman analysis to evaluate equation estimated daily urine volume from spot urine creatinine, demographic variables, and body weight in patients with or without nephrolithiasis. We hypothesized this equation could accurately estimate daily urine output in outpatients with nephrolithiasis.

Results: Among persons submitting specimens to Litholink Laboratories between May 2013 and January 2016, we identified 19,884 individuals who had two 24 hour urine collections on consecutive days, with creatinine excretion rates ±10%. We used Pearson correlations and Bland-Altman analysis to evaluate equation estimated daily urine volume from spot urine creatinine, demographic variables, and body weight in patients with or without nephrolithiasis. We hypothesized this equation could accurately estimate daily urine output in outpatients with nephrolithiasis.

Conclusions: A simple equation using urine creatinine, demographics and body weight in patients with or without nephrolithiasis could be used to estimate daily urine output and worthwhile studies in larger group of people with and without stone disease. We hypothesized this equation could accurately estimate daily urine output in outpatients with nephrolithiasis.

Funding: NIDDK Support
**PO1111**

**Attenuated Urinary Sodium and Volume in Response to Saline Load in Heart Failure with Preserved Ejection Fraction**

Adhish Agarwal,1 Srinivasan Beddhu,1 Robert E. Boucher,1 Nirupama Ramkumar,1 Aylin R. Rodan,1 Veena Rao,1 Habeeb Mohammad,1 Elizabeth Dranow,1 Guo Wei,1 Kevin S. Shah,1 James C. Fang,1 Alfred K. Cheung.1

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**Background:** Heart failure (HF) is characterized by fluid overload due to impaired sodium (Na) excretion. Impaired urinary Na excretion in response to intravenous Na load has been demonstrated in HF with reduced ejection fraction (HFrEF). We hypothesized that patients with HF with preserved ejection fraction (HFP EF) also have impaired urinary sodium excretion and volume in response to intravenous Na load.

**Methods:** All participants were instructed to follow a low (2-3 g/d) sodium diet for a week prior to the study. Urinary results were normalized using urine creatinine. Cases and controls were compared using Wilcoxon rank-sum tests.

**Results:** Mean age and body mass index for the HFpEF participants were 62±12 years and 36.3±8.5 Kg/m², and for control participants were 47±18 years and 24.6±3.7 Kg/m² respectively. Plasma BNP tended to be higher (median 54.0 (29.0, 118.0) versus 5.0 (5.0, 34.0) pg/ml; p = 0.15), while ucGMP/plasma BNP ratio was lower (median 0.7 (0.4, 0.8) versus 7.3 (1.7, 8.5) (pmol/mg)/(pg/ml); p = 0.014) in cases as compared to controls.

**Conclusions:** In this rigorous, controlled human pilot study, patients with HFP EF had lower urinary volume and attenuated urinary sodium excretion compared to controls after intravenous sodium and volume load. Data and biospecimens collected in this study should inform the pathogenesis of sodium retention in HFP EF.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**PO1112**

**Attenuated Renal Response to Endogenous Natriuretic Peptides in Heart Failure with Preserved Ejection Fraction**

Adhish Agarwal,1 Srinivasan Beddhu,1 Robert E. Boucher,1 Nirupama Ramkumar,1 Aylin R. Rodan,1 Veena Rao,1 Habeeb Mohammad,1 Elizabeth Dranow,1 Guo Wei,1 Kevin S. Shah,1 James C. Fang,1 Alfred K. Cheung.1

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**Background:** The pathophysiology of sodium retention in heart failure with preserved ejection fraction (HFP EF) remains largely unknown. A potential mechanism is attenuated renal response to natriuretic peptides (NPs). Urinary cyclic guanosine monophosphate (ucGMP) is an intracellular messenger of NPs, and an attenuated ucGMP/B-type NP (BNP) ratio suggests decreased renal response to BNP. We hypothesized that patients with HFP EF have attenuated response to NPs.

**Methods:** We studied ucGMP/plasma BNP ratios in 9 HFP EF patients and 5 controls (no history of renal or heart disease). All participants were placed on a low (2-3 g/d) sodium diet for a week prior to the study. Urinary results were normalized using urine creatinine. Cases and controls were compared using Wilcoxon rank-sum tests.

**Results:** Mean age and body mass index for the HFP EF participants were 62±12 years and 36.3±8.5 Kg/m², and for control participants were 47±18 years and 24.6±3.7 Kg/m² respectively. Plasma BNP tended to be higher (median 54.0 (29.0, 118.0) versus 5.0 (5.0, 34.0) pg/ml; p = 0.15), while ucGMP/plasma BNP ratio was lower (median 0.7 (0.4, 0.8) versus 7.3 (1.7, 8.5) (pmol/mg)/(pg/ml); p = 0.014) in cases as compared to controls.

**Conclusions:** Our pilot study shows that ucGMP/plasma BNP ratio, which reflects renal response to BNP, was attenuated in patients with HFP EF. These data suggest that impaired renal response to NPs may be implicated in the pathogenesis of fluid retention in HFP EF.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**PO1113**

**Association of Urinary Potassium Excretion with Progression of CKD**

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**Background:** Out of range serum potassium levels are associated with worsening renal function and increased occurrence of cardiovascular disease (CVD) events in...
chronic kidney disease (CKD). However, conflicting results have been reported regarding the protective value for adverse health outcomes of urinary potassium excretion. Therefore, we conducted a cohort study to determine whether urinary potassium excretion is an independent risk factor for renal function deterioration or increased CVD events.

Methods: We identified 650 patients with pre-dialysis CKD who were hospitalized for CKD educational program between 2010 and 2018. Study outcomes analyzed were CKD progression and incidence of CVD events. Baseline urinary potassium to creatinine ratio (UK/Cr, expressed as mmol/gCr) was ranked into quartiles as follows: Q1, <19.8; Q2, 19.9–27.7; Q3, 27.8–37.9; and Q4, >38.0.

Results: During follow-up (median 35 months), 509 CKD progression and 129 CVD events were identified. Further, 62 patients died during follow-up. Multivariate Cox models showed that an increased risk of CKD progression was observed in patients with low UK/Cr compared to those with high UK/Cr, after adjustment for demographic factors and laboratory data. In a fully adjusted model, adjusted hazard ratios (HRs) with the fourth (highest) quartile as reference category were 2.02 (95% CI, 1.50–2.71), 1.34 (95% CI, 1.02–1.77), and 1.14 (95% CI, 0.87–1.50), for Q1–3 respectively (trend: P < 0.001). Similarly, an inverse probability weighting analysis showed an increased risk of CKD progression in Q1 and Q2 compared with Q4. We did not observe any significant modification in subgroup analyses. Furthermore, consistent association was confirmed between lower fractional excretion of potassium and worsening renal function. However, UK/Cr had no association with the incidence of CVD events.

Conclusion: A low UK/Cr is independently associated with worsening renal function but not with an increased risk of a CVD event in patients with pre-dialysis CKD.

POI1114
Licorice-Induced Syndrome of Mineralocorticoid Excess
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Introduction: Edema and volume overload are common complaints. Here, we present a case of hypertension and potassium wasting due to licorice ingestion.

Case Description: A 34 y/o Caucasian woman with significant history for hypothyroidism and recurrent episodes of bronchitis presented for evaluation of recurrent cough, fever, and exacerbation of her chronic bronchitis. On examination, she was found to have a blood pressure of 139/72 mmHg. A urinary sodium test revealed a sodium level of 139 mmol/L. A 24-h urine study revealed a urine sodium level of 30 mmol/L. A urine sample was sent for a licorice level, which returned at 40 mg/mL. The patient denied licorice ingestion.

Discussion: Chronic ingestion of licorice is a rare but known cause of syndrome of mineralocorticoid excess (AME). Licorice contains a steroid, glycyrrhetinic acid, which inhibits the function of the enzyme 11-beta-HSD2. This same enzyme is deficient in mineralocorticoid excess (AME). Licorice contains a steroid, glycyrrhetinic acid, which inhibits the function of the enzyme 11-beta-HSD2. This same enzyme is deficient in mineralocorticoid excess (AME). This can occur at even low amounts of licorice ingestion. The patient was treated with cessation of licorice, and the sodium level returned to normal levels. The patient was discharged with no further licorice ingestion.

POI1115
Not Just Licorice: Abiraterone and Apparent Mineralocorticoid Excess
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Introduction: Abiraterone is a CYP17A1 inhibitor which blocks androgen synthesis and is used to treat castration-resistant prostate cancer. This drug also decreases cortisol synthesis, causing a compensatory increase in adrenocorticotropic hormone (ACTH) and accumulation of mineralocorticoids. The result is the syndrome of apparent mineralocorticoid excess (AME) which manifests clinically as hypokalemia, metabolic alkalosis and hypertension. Abiraterone is approved for use only with concurrent medical treatment to prevent or treat these effects. We present a case of refractory hypokalemia resulting from abiraterone use.

Case Description: A 74-year-old man with metastatic prostate cancer and neck cancer presented with urinary retention and acute kidney injury (AKI) as well as hypertension and metabolic alkalosis which were present a week prior. Home medications included abiraterone, ciplatin (given two weeks prior), prednisone 5 mg daily (recently decreased from 5 mg twice daily) and spironolactone. A urinary catheter was placed, the AKI improved rapidly and the patient remained with refractory hypokalemia. A urine potassium-to-creatinine ratio was high. Post-obstructive polyaury was considered as a reason for kaliuresis; however, hypokalemia and metabolic acidosis preceding this event made it unlikely to be the sole cause. Given abiraterone use, serum cortisol was checked and was low with no increase after giving cosyntropin. Serum aldosterone, renin and their ratios were normal. The patient was diagnosed with abiraterone-induced AME. Prednisone was increased to 5 mg twice daily and eplerenone was started in place of spironolactone.

Two months later, the serum potassium was normal without supplementation.

Discussion: Abiraterone-induced AME is characterized by low serum cortisol but unlike adrenal insufficiency, presents with hypokalemia, metabolic alkalosis and hypertension. In this case, AME resulted from inhibition of the 17α-hydroxylase activity of the CYP17A1 enzyme, leading to decreased cortisol, increased ACTH, and accumulation of the potent mineralocorticoid deoxycorticosterone. Glucocorticoid supplementation (prednisone 5 mg twice daily recommended) is needed to suppress ACTH and prevent these effects. Eplerenone is an adjunct and is preferred over spironolactone in patients with castrate-resistant prostate cancer as spironolactone interacts with the androgen receptor.

POI116
Jägermeister-Induced Pseudohyperaldosteronism
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Introduction: Hypertension and hypokalemia is known to be caused by hyperaldosteronism. We report a case of hypertension, hypokalemia, and suppressed renin and aldosterone levels. Dietary work-up revealed copies ingestion of Jägermeister liquor which contains licorice, a known cause of pseudohyperaldosteronism.

Case Description: A 54-year-old man with a history of HIV on Genvoya and CAD, HTN on metoprolol and isosorbide monoate was referred to nephrology for evaluation of hypokalemia and accelerated hypertension. Prior to nephrology referral, he was started on oral potassium for 6 weeks and the repeat potassium was 3.5 mmol/L. On review of systems, he had no specific complaints except occasional diarrhea. On exam, his BP was 190/110, 1+ lower extremity edema; his exam was otherwise unremarkable. Initial workup revealed serum sodium 143 mmol/L, bicarb 24 mmol/L, potassium 3.5 mmol/L, creatinine 1.1 mg/dL, magnesium 1.5 mg/dL, calcium 1.0 mmol/L, uric acid 7.1 mg/dL, Fek 13.6%, TSH 2.95 uIU/mL, plasma renin activity 1.191 ng/mL/hr, and aldosterone <3.0 ng/dL, and plasma metanephrines <10 pg/mL. Repeat K was 3.1, bicarb 30, plasma renin activity 0.195 ng/mL/hr, and aldosterone <3.0 ng/dL; urine K 34, FeK 11%; renal dopplers without evidence of RAS. Given hypokalemia, metabolic alkalosis with evidence of potassium wasting, and suppressed renin and aldosterone levels, a thorough dietary review was conducted which revealed chronic Jägermeister ingestion of up to 500 mL per day. He stopped drinking Jägermeister and on subsequent follow-up, his BP was controlled on atenolol, carvedilol, and isosorbide mononitrate, and he no longer required potassium supplementation.

Discussion: Licorice contains glycyrrhizic acid which inhibits 11 beta-hydroxysteroid dehydrogenase, preventing inactivation of cortisol to cortisone, and resulting in excess mineralocorticoid activity manifested by suppressed renin and aldosterone levels, sodium retention, hypokalemia, hypertension, and edema. According to the manufacturer, Jägermeister liquor contains under 10 mg/L of licorice, however, the amount that can cause toxicity is not certain and literature suggests that the glycyrrhizic acid content of licorice is widely variable. Physicians ought to consider dietary, non-medication causes for electrolyte abnormalities in patients with initial negative workups.

POI117
Posaconazole-Related Mineralocorticoid Excess in a Patient with Acute Myeloid Leukemia
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Introduction: Posaconazole is an antifungal used for treatment and prophylaxis of invasive fungal infections in cancer patients. We report a case of posaconazole related mineralocorticoid excess in a patient with acute myeloid leukemia (AML).

Case Description: A 58-year-old male with past medical history of relapsed AML status post stem cell transplant, was admitted on 08/16/2020 to UTMDACC for pain, nausea, vomiting, diarrhea, and fatigue. He developed multiple complications streptococcus viridans bacteremia, candidemia, Graft Versus Host Disease, disseminated intravascular coagulation, fungal pneumonia, tracheostomy, transplant-associated respiratory failure, and hepatitis B with HSV-1 on Foscarnet. Nephrology was consulted for hyponatremia, hypokalemia and alkalosis. No nausea, vomiting, diarrhea was reported. Due to a combination of hypertension, metabolic alkalosis, hypokalemia and being on Posaconazole, we suspected
Pseudo-hyperaldosteronism. Renin, aldosterone levels were checked which are low. CT scan of abdomen was not reported the same. Renal function test was negative and aldosterone was high. Hypokalemia and hyperkalemia was noted and aldosterone level was raised. CT scan revealed hyperplasia of the adrenal gland.

Discussion: Combination of hypokalemia, hypertension and metabolic alkalosis need to suspect mineralocorticoid excess. Posaconazole inhibits 11 beta-hydroxysteroid dehydrogenase type 2 which prevents conversion of cortisol to cortisone. Fracassos and aldosterone leads to amplification of mineralocorticoid receptor action causing increase in activity, number of epithelial sodium channels (ENaC), Na-K-ATPase channels. Excess uptake of sodium leads to hypertension and creates increased negativity causing K+ and HCO3- uptake. Hypokalemia leads to alkalosis and patient was hypertensive due to hyperkalemia. Patients with mineralocorticoid excess can be treated with aldosterone receptor antagonist or ENaC blockers or by stopping or decreasing the dose of Posaconazole. Patients on posaconazole need to be monitored for hypokalemia, hypertension and alkalosis. However, not every patient will develop these which may be likely due to genetic predisposition.

PO1118
Prednisolone-Related Mineralocorticoid Excess: Case of Hypokalemia and Metabolic Alkalosis
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Introduction: We report a case of the mineralocorticoid effect of prednisolone resulting in hypokalemia and metabolic alkalosis. This is rare due to the lack of aldosterone deficiency in patients with prednisolone use.

Case Description: A 78 year-old male with past medical history of oropharyngeal squamous cell carcinoma presented with fatigue. One week prior, he was treated with pembrolizumab. Admission vital signs were significant for fever to 39.1°C and normotensive blood pressure 130/88. Laboratory results revealed serum potassium (K+) 4.1 mmol/L, bicarbonate (HCO3-) 26 mmol/L and newly elevated liver enzymes. He was diagnosed with immune checkpoint inhibitor hepatitis and treated with prednisolone 70 mg via nasogastric tube (NGT). Two days later, blood pressure increased to 170/80 and laboratory studies revealed hypokalemia and metabolic alkalosis. The triad of hypokalemia, metabolic alkalosis and hypertension lead us to suspect a hyper mineralocorticoid state. Workup revealed spot urinary aldosterone of 8 ng/mL and aldosterone 8 ng/dL. Patient was then started on aggressive intravenous and oral potassium repletion. He continued to require multiple doses of intravenous potassium to maintain potassium levels of 3.5 mEq/L. He was subsequently started on Eplerenone on Day 3 of admission with excellent response. He remained otherwise asymptomatic from COVID and as his infection improved, hypokalemia stabilized and he was ultimately discharged with a Potassium level of 3.6 mEq/L.

Discussion: The primary defect in BS is in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle resulting in hypokalemia, metabolic alkalosis and secondary hyperaldosteronism. Rare cases of acquired BS are reported in association with tuberculosis, sarcoidosis, sjogrens, and certain drugs. All of these were ruled out in our patient and hence a diagnosis of idiopathic BS like phenotype was made. In our patient, we attribute the BS like phenotype to underlying COVID infection. As his infection improved, his hypokalemia also resolved. Hyperkalemia is a more common finding in COVID infection. However, in our patient, hypokalemia secondary to BS like phenotype was a unique presentation which was challenging to treat. In the absence of usual findings of acquired BS like phenotype, the patient with COVID infection should prompt suspicion for BS-like phenotype. Early and aggressive correction of electrolyte abnormalities is crucial.

PO1119
From Hypokalemia to Sjogren Syndrome: What a Twist!
Elisabeth Pabon-Vazquez, Jose Rivera Sepulveda. Mayaguez Medical Center, Mayaguez, Puerto Rico.

Introduction: Potassium disorders are one of the many serious conditions that could attempt against a patient’s life. Understanding the clinical presentation, diagnosis, management and the role of hypokalemia and treatments of hypokalemia are essential for the development of successful clinical physician. In addition, being aware of the associations between electrolyte disturbances and rheumatologic conditions increases the benefits of correctly treating and preventing underlying problems.

Case Description: This is the case of a 24 y/o female patient, G1P2A0, with a past medical history of hypoglycemia and hypokalemia since pregnancy with twins. Patient presented to emergency department with shortness of breath, general malaise, muscle weakness, and unable to ambulate. Physical examination was remarkable for proximal muscle weakness, decreased deep reflexes with intact sensation. Laboratory bloodwork revealed positive mycoplasma pneumonia infection, normal anion gap metabolic acidosis with severe bicarbonate and potassium deficiency with EKG changes as well hypertension.

Discussion: Pseudohypokalemia is associated with a variable degree of disease severity. The mutation types have been identified as large deletions, missense and nonsense mutations. This patient likely has type 3 BS but with a variable degree of disease will be used to suppress the high level of PGE2 associated with the disease.

PO1120
Idiopathic Bartter Syndrome-Like Phenotype Diagnosed in a Diabetic Patient with COVID-19 Infection
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Introduction: Bartter syndrome (BS) is a rare genetic tubulopathy affecting the loop of Henle leading to salt wasting. Acquired BS is very rare and is associated with underlying medical conditions or variants. We report a unique case of idiopathic BS-like phenotype that was diagnosed in the setting of COVID infection.

Case Description: A 71-year-old man with coronary artery disease, hypertension and diabetes presented after a mechanical fall. On admission, he was found to be hypotensive to 107/88 mmHg. Physical exam was within normal limits. Initial blood work was significant for Potassium 2.6 mEq/L, Bicarbonate 34 mEq/L, Calcium 8.0 mg/dL and Magnesium 1.7 mg/dL. Patient also tested positive for COVID-19. Upon further questioning, patient reported a remote history of hypokalemia but never needed any electrolyte supplementation. He denied diuretic use or surrepitious vomiting. Hypokalemia work up revealed increased urinary potassium of 85.4 mEq/L. Renin 15.72 ng/mL/hour and Aldosterone 8 ng/dL. Patient was then started on aggressive intravenous and oral potassium repletion. He continued to require multiple doses of intravenous potassium to maintain potassium levels of 3.5 mEq/L. He was subsequently started on Eplerenone on Day 3 of admission with excellent response. He remained otherwise asymptomatic from COVID and as his infection improved, hypokalemia stabilized and he was ultimately discharged with a Potassium level of 3.6 mEq/L.

Discussion: The primary defect in BS is in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle resulting in hypokalemia, metabolic alkalosis and secondary hyperaldosteronism. Rare cases of acquired BS are reported in association with tuberculosis, sarcoidosis, sjogrens, and certain drugs. All of these were ruled out in our patient and hence a diagnosis of idiopathic BS like phenotype was made. In our patient, we attribute the BS like phenotype to underlying COVID infection. As his infection improved, his hypokalemia also resolved. Hyperkalemia is a more common finding in COVID infection. However, in our patient, hypokalemia secondary to BS like phenotype was a unique presentation which was challenging to treat. In the absence of usual findings of acquired BS like phenotype, the patient with COVID infection should prompt suspicion for BS-like phenotype. Early and aggressive correction of electrolyte abnormalities is crucial.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO1122

Colonial Pseudo-Obstruction and Hypokalemia
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Introduction: Ogilvie’s syndrome, or colon pseudo-obstruction, is the pathologic dilation of the colon without underlying mechanical obstruction. It is caused by increased sympathetic activity or reduced parasympathetic activity. The common manifestation in constipation, but sometimes it may be associated with diarrhea when potassium secretion is greatly increased by stretch-activated maxi-K channel, also known as BK channel, resulting from dilatation of the colon. While exact mechanism is unclear, diagnosis is based on clinical and radiologic grounds.

Case Description: A 69 year old African American female with history of diabetes mellitus, hypertension, hyperlipidemia, and HIV infection presented with worsening lower back pain. Initial labs showed leukocytosis, anemia, mild renal impairment, and paraproteinemia. MRI of the spine showed extensive compression deformities and epidural extension, with lytic lesions on skeletal survey. Bone biopsy showed >80% blast cells with marked increase in circulating plasma cells, confirming plasma cell leukemia. Abdominal CT showed dilated ascending colon suggestive of obstruction, but she was having normal bowel movements. She successfully underwent induction therapy and was discharged. When she was readmitted for second cycle of chemotherapy, serum potassium of 1.8 mmol/L with U wave on ECG noted. She also complained of abdominal distension, diarrhea, and bilateral lower extremity edema. Despite aggressive potassium supplementation, her potassium level persistently remained below 3.5 mmol/L. Initial urine potassium was 23 mmol/L, which peaked at 45.8 mmol/L before becoming anuric. First stool potassium was >100 mmol/L with stool volume of 900 mL. Repeat stool study after a week showed stool potassium 59.5 mmol/L with stool sodium 42 mmol/L. Abdominal x-ray on admission showed colon distension measuring up to 11.4 cm at the cecum. Serial imaging of the bowel showed worsening diffused colonic dilation. Remarkably, our patient required large doses of potassium supplement while she remained anuric.

Discussion: Colon pseudo-obstruction may result in, some patients, in dramatic upregulation of the maxi-K channel. When potassium secretion is greatly increased, diarrhea rather than constipation becomes predominant manifestation. Diarrhea is the result of high potassium content of the stool, unlike most other secretory diarrhea which contains sodium as the main cation.

PO1123

Prevalence and Recurrence of Hyperkalemia (HK) in Medicare Patients Admitted to Long-Term Care or Post-Acute Care (LTC/PAC) Settings
James F. Neumenschwander,1 Alison R. Silverstein,2 Christie Teigland,1 Dakota C. Powell,2 Shambhavi Kumar,3 Jill Dreyfus,2 Edric Y. Zeng,2 Abiy Agiro,3 William Potter,2 and William Peacock,1
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Background: Hyperkalemia is a frequently encountered electrolyte disorder usually resulting from decreased dietary intake, gastrointestinal, and/or renal wasting. In distal tubule cells, with no lysine (WNK) kinases bind with Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) to form WNK bodies. Tubule cells, with no lysine (WNK) kinases bind with Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) to form WNK bodies. In distal tubule cells, with no lysine (WNK) kinases bind with Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) to form WNK bodies.

Methods: This retrospective study used 100% Medicare Fee-For-Service data for patients age ≥65 with ≥1 LTC/PAC stay from 01/2017 to 11/2019; index date was admission date of first LTC/PAC stay. HK-related stay was defined as ≥1 HK diagnosis (ICD-10: E87.5) or evidence of potassium binder use during LTC/PAC stay or within 14 days pre-index. Baseline characteristics and prevalence of HK during 1 year of follow up among HK index stays were compared to non-HK index stays. HK index stays were stratified into 3 cohorts; CHF, CKD or end-stage renal disease (ESRD), and CHF+CKD/ESRD.

Results: Of 4,562,231 patients with ≥1 LTC/PAC stay, prevalence of HK during pre-index, index, or follow up periods was 14.7%. The final sample (4,081,103) excluded patients with an HK event only during follow up. Of the final cohort, 290,567 (7.1%) of index stays were HK-related. All-cause (HK-related) index stays consisted of 54.0% (46.5%) LTC/PAC stays, 27.8% (41.4%) skilled nursing facilities, 6.7% (8.8%) inpatient rehabilitation facilities, and 0.9% (3.1%) long term acute hospital settings. HK vs non-HK patients were more often male (43.0% vs 35.4%), Black (13.5% vs 8.0%), and dual eligible for Medicaid (34.2% vs 25%), with higher mean Charlson Comorbidity Index scores (6.19 vs 3.93). Mean annual HK event during follow up were highest in patients with CHF+CKD/ESRD (all patients=1.47; HK=6.98), followed by CKD (0.66; 5.53), and CHF (0.18; 3.00), with similar patterns across settings. In the HK cohort, 34.5% had HK recurrence during follow up; 2.7% filled a potassium binder prescription during index LTC/PAC stay, and 4.3% did not.

Conclusions: HK patients were more often non-White and low income, indicating possible disparities in care. Prevalence and recurrence of HK was high among patients with LTC/PAC stays, but few patients filled a potassium binder prescription, suggesting potential gaps in treatment during or after an LTC/PAC stay.

Funding: Commercial Support - AstraZeneca

PO1124

Impact of Hyperkalemia and the Disruption of Emergencies and Surgical Care
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Background: Due to the increasing prevalence of kidney disease, hyperkalemia (HK) may be diagnosed with greater frequency in Surgical and Emergency Departments (ED). Despite this, specific guidelines do not exist and patients with elevated potassium (K+) are typically managed on a case by case basis.

Methods: An anonymous structured survey was emailed to (~11,287) clinicians in the Advocate Aurora Health system regarding HK knowledge and treatment paradigms (n=237 responded). Survey was conducted from Feb to March 2021.

Results: Nearly half (47%) of respondents treat ≥ 10 HK patients annually, with most common diagnosis of HK occurring in the ED (43.8%) and OR (23%) setting. HK was considered a significant concern by 47% of respondents at a serum K+ level of 5.6-5.9 mEq/L and by 39% at K+ ≥ 6.0 mEq/L. Only 50% of respondents recognized RAASi medications as a potential risk factor for HK. IV fluids and keyesalate were the two most common treatments for HK. Limitations to pharmacological management included the need to monitor potassium, patient compliance, and time of onset. In the survey surgery, 66% felt that K+ more than 5.5 mEq/L on day of surgery will lead to cancellations and 52% believed pharmacologic agents having a shorter onset of action may reduce surgery cancellations and delays. Vascular (34%) and general (30%) surgeries were reported to be most impacted by HK. 82% stated urgent dialysis is difficult to arrange and admission is inevitable for dialysis.

Conclusions: The presence of HK creates challenges to ED or surgical clinical teams to manage and avoid cancellations. Standard treatment options for lowering serum K+ are limited due to time of onset and compliance considerations. Dialysis is difficult to arrange on short notice and almost always requires patient admission. In cases of emergent HK, newer K+ binding agents having a more rapid onset of action to lower serum K+, may reduce avoidable admission, surgical cancellation, and delay of surgery. More evidence-based care is needed in surgical settings to characterize patients at high risk for HK to prevent unnecessary surgical cancellation and limit health care costs.

Funding: Commercial Support - AstraZeneca
similar observation of transient hyperkalemia seen in a case published in 1953 of a young woman treated for chronic hypokalemia (Sciarrino, 1953). Critical hyperkalemia is an important consideration when treating patients with chronic hypokalemia.

POI1126

Potassium Hyperkalemia with Concurrent Hyperkalemia

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Introduction: In sickle cell patients, acute hematologic crisis and sickle cell nephropathy are relatively common. Risk of hyperkalemia increases with hemolysis and tubular dysfunction. Sepsis can also worsen the complication of hemorrhagic crisis with significant thrombocytopenia, a well-known cause of pseudohyperkalemia. We report a case of concurrent true hyperkalemia and pseudohyperkalemia in the setting of thrombocytosis due to acute sickle cell crisis.

Case Description: A 36 year old African American male with history of sickle cell disease, asthma and DVT presented with bilateral shoulder, knee, and back pain. In ED, he was hypertensive, and tachycardic. Labs were notable for leukocytosis, anemia, reticulocytosis, renal failure, and elevated lactate dehydrogenase. Chest x-ray showed left base atelectasis. He was admitted for acute sickle cell crisis and fluctuant right thigh abscess, which was surgically drained and managed with antibiotics. Platelet level was 585 K/ul, serum potassium was 4.7 mmol/L, and creatinine was 1.78 mg/dl. With normal urine output. Potassium level steadily rose and peaked at 6.5 mmol/L with sinus bradycardia but no other ECG changes. At the same time, platelet level peaked to 1105 K/ul.

Discussion: In our patient with significant thrombocytosis, pseudohyperkalemia was suspected. Degranulation of platelets during clotting releases about 50% of potassium inside platelets. For platelet count of 1000 K/ul, with normal MPV, serum potassium is expected to be higher than plasma potassium level by about 0.7 mEq/L. Serum-plasma potassium differences in our patient were within the expected range. In our patient, as shown below, mild concurrent true hyperkalemia is also noted likely due to sickle cell nephropathy, a known cause of hyperkalemia due to hyperreninemic hypoaldosteronism. Due to potassium release from platelets during clotting, serum potassium is always higher than plasma potassium in all normal persons by 0.2 to 0.3 mmol/L. With thrombocytosis, the difference becomes larger, and serum potassium is likely to reach hyperkalemic level if the baseline potassium is already higher than usual due to concomitant impairment of renal potassium excretion.

POI1127

Missing the Obvious? A Story of Salt, Water, and Unexplained Hyperkalemia

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Introduction: Most clinicians are familiar with the differential diagnosis of hyperkalemia, from pseudohyperkalemia to rare tubulopathies. Herein, we describe three patients with years-long histories of unexplained hyperkalemia despite extensive investigations (details in Table 1). While all achieved normokalemia with various prescription regimens, the underlying etiology remained elusive. We suggest that all cases were likely due to chronic, mild hypovolemia in the context of self-imposed dietary salt restriction.

Case Description: Patient A: A 6-week-old girl with persistent hyperkalemia and very low urine Na+. Normokalemia was achieved with hydrochlorothiazide and dietary K+ restriction but maintained with optimized fluid and Na+ intake alone. Patient B: An 11-year-old boy with spastic cerebral palsy with persistent hyperkalemia after a mild AKI attributed to thalidomide. Serum K+ improved with sodium polystyrene (SPS) resins and dietary K+ restriction; it normalized after 5 days of intravenous infusion, while SPS. Patient C: A 5-month-old boy with Stüve-Wiedemann Syndrome and feeding difficulties with persistent hyperkalemia that normalized on SPS. After G-tube insertion at 2 years, K+ remained normal despite stopping the SPS due to improved fluid and Na+ intake.

Discussion: It has long been established that adequate Na+ and fluid delivery to distal nephrons is necessary for optimal K+ handling. It is therefore surprising to find almost no mention of Na+-responsive hyperkalemia in the literature for children beyond the neonatal period. Our patients all had hyperkalemia in the context of normotension, but very low fractional excretion of Na+ (FeNa) and low trans-tubular K+ gradient (TTKG). They all remained normokalemic when salt and water intake was optimized, despite stopping their hyperkalemic prescriptions. Careful, early consideration of low distal Na+ and water delivery as a cause for unexplained hyperkalemia could prevent extensive workups and unnecessary prescriptions.

POI1128

Machine Learning Models to Predict Cardiovascular and Renal Outcomes and Mortality in Hyperkalemic Patients

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Background: Hyperkalemia is associated with increased risks of mortality and adverse clinical outcomes. To date, limited evidence is available for personalized risk evaluation in this heterogeneous and multifactorial pathophysiological conditions. Methods: We developed prediction models using extreme gradient boosting (XGB), logistic regression (LR), and neural network. Models were derived and cross-validated in a retrospective cohort of hyperkalemic patients with either heart failure or stage ≥3 chronic kidney disease and aged ≥18 years from a Japanese administrative hospital database (April 1, 2008–September 30, 2018). The outcomes of interest included all-cause death, introduction of renal replacement therapy (RRT), hospitalization for heart failure (HHF), and cardiovascular events within 3 years after first hyperkalemic episode. The best performing model was further validated using a separate hospital-based database. Results: 24,949 adult patients with hyperkalemia were selected for the model derivation and internal validation. The mean age was 75 years and 54% were male. Among machine learning algorithms tested, XGB outperformed other models, showing AUROC of XGB vs. LR for all-cause death, RRT, HHF, and cardiovascular events as 0.823 vs. 0.809, 0.957 vs. 0.947, 0.863 vs. 0.838, and 0.809 vs. 0.838, respectively. In the external validation set including 86,279 patients, AUROC of XGB for all-cause death, RRT, HHF, and cardiovascular events were 0.947, 0.988, 0.673, and 0.585, respectively. The Kaplan-Meier curves of high-risk predicted group showed a significant differentiation from that of low-risk predicted group for all outcomes (Figure).

Conclusions: These findings suggest the possible use of machine learning models for real-world risk assessment as a guide for treatment decision making that may lead to the improvement of cardiovascular and renal outcomes, and mortality in hyperkalemic patients.

Funding: Commercial Support - AstraZeneca K.K.

POI1129

Severe Hyperkalemia Secondary to Hypermagnesemia in a Patient with Preeclampsia

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Introduction: Mg infusion remains the first-line treatment of preventing and controlling eclamptic seizures. While hypekalemia is a well-known side effect, hyperkalemia is not. We present a case of severe hyperkalemia secondary to magnesium infusion requiring hemodialysis.

Case Description: 36-year-old healthy female with no HTN or liver disease, pregnant at 25 weeks with twins, admitted for close monitoring given concern for intra-uterine growth restriction. Initial vitals on admission: BP 149/88 mm Hg, HR 89,
Changes in potassium and calcium concentrations in relation to hypermagnesemia (figure 1)

POI130
Severe Hypermagnesemia: A Potential Cause of Acute Hyperkalemia
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Introduction: Hypermagnesemia is not a well-established cause of hyperkalemia. In this case report we explore the association of acute hypermagnesemia and hyperkalemia.

Case Description: 30 year old female G1P0 with chronic HTN since age 26, CACUT was admitted for preeclampsia with severe features (new proteinuria 5.5 g/24h). Hypermagnesemia developed (peak 8), she simultaneously developed acute hyperkalemia (peak K 6.1, bicarb 19, lactate 85). Creatinine was normal at 0.7. Mg infusion was stopped. Other etiologies for hyperkalemia were ruled out including rhabdomyolysis or worsening hemolysis. The patient required one session of emergent hemodialysis which led to improvement in all electrolyte abnormalities.

Discussion: While the relationship between hypomagnesemia and hypokalemia is well understood, the relationship between hyperkalemia in the presence of hypermagnesemia remains not clear. Some of the mechanisms suggested (1) direct effect of magnesium on suppressing renin and aldosterone leading to impaired renal handling of K homeostasis (hyporeninemic hypoaldosteronism). (2) direct inhibition of the ROMK channel by Mg.

Conclusion: Severe hypermagnesemia can lead to acute hyperkalemia which can be life threatening. Close monitoring of serum electrolytes is advised.

POI131
When Sipping K Is Not OK
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Introduction: Hyperkalemia is one of the most common and potentially lethal electrolyte abnormalities that occurs in approximately 1% to 10% of hospitalized patients. It is associated with an increased risk of arrhythmias, poor cardiovascular outcomes, and increased morbidity and mortality. We highlight an unusual etiology of severe hyperkalemia in a patient with underlying CKD.

Case Description: A 74-year-old Black male with known arterial hypertension, coronary artery disease, CKD 3 [baseline serum creatinine (Cr) 1.7 mg/dl] presented with syncope secondary to severe bradycardia (heart rate 30/min) consequent to severe hyperkalemia, which necessitated a pacemaker placement, and non-oliguric AKI on CKD. Pertinent serum labs on presentation include Cr 2.8 mg/dl, potassium (K) 7.6 mmol/L, and bicarbonate 19 mmol/L. Serum osmolality, glucose, and creatinine kinase levels were within normal limits. Urine pH was 5. Renal imaging was unremarkable. He was not on any medication(s) commonly attributed with a propensity to elevate serum K, including renin angiotensin inhibitors, non-selective β blockers, or non-steroidal anti-inflammatory agents. Given that the hyperkalemia was out of proportion to his kidney injury, upon further questioning he attributed consuming a diet rich in K along with drinking multiple cups of Essiac tea daily for the last 2 months. Hyperkalemia was managed medically, including initial temporizing measures, bicarbonate supplementation, K binders, and intravenous crystalloids to enhance distal nephron K excretion. Placement was placed on consuming a K restricted diet along with discontinuing Essiac tea use. Serum K normalized in 3 days; however, Cr was 3 mg/dl on discharge.

Discussion: Essiac tea contains red clover, sheep sorrel, burdock root, and rhubarb which has extremely high potassium content. It is hepatotoxic and nephrotoxic when consumed in large amounts. We highlight the importance of obtaining a thorough dietary history, especially when the degree of hyperkalemia cannot be solely attributed to the extent of kidney injury. Dietary counselling is paramount in such cases.

POI132
Metabolic Acidosis That Exists with Hyperkalemia (HK) Among Patients That Initialize Binder Therapy: The MAXIMIZE Study
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Background: Approximately 25% of chronic kidney disease (CKD) patients with serum potassium (sK+) >5.0 mEq/L may also have metabolic acidosis (MA). However, successful management of comorbid HK and MA in CKD patients is unclear. This real-world evidence study examines the association between patient characteristics and binder treatment among CKD patients with HK and MA.

Methods: This was a retrospective study of stage 3-5 CKD patients with HK (sK+ >5.0 mmol/L) and MA (serum bicarbonate (sHCO3-)<20 mmol/L; OR=1.29 (1.03-1.61); OR=1.24 (1.04-1.47)) and liver disease (OR=1.61 (1.16-2.23); OR=1.47 (1.14-1.89)), respectively. Treatment with sHCO3-<20mmol/L in a US EMR network of 64 million patients. The index event was the first qualifying sK+ between 07/01/19 and 12/31/20. Baseline demographic and clinical characteristics were assessed among SZC, SPS, and NKB treated cohorts including age, sex, race, HK severity, sHCO3- level, visit type, and comorbidities. Logistic regression produced adjusted odds ratios (ORs) and 95% confidence intervals describing the association between baseline characteristics and treatment: sodium zirconium cyclosalicate (SZC) vs sodium polystyrene sulfonate (SPS) and SZC vs no potassium binder (NKB).

Results: Of the 32,113 patients who met study criteria 11.6% were treated with SZC (n=3,572). Age and sex were similar among SZC, SPS, and NKB cohorts and 81%, 77%, and 70% had moderate-to-severe acidosis (sHCO3- <20mmol/L), respectively. Baseline characteristics associated with increased odds of SZC vs SPS and SZC vs NKB treatment included sHCO3-<20mmol/L [OR=1.29 (1.03-1.61); OR=1.24 (1.04-1.47)] and liver disease [OR=1.61 (1.16-2.23); OR=1.47 (1.14-1.89)], respectively. Treatment with SZC vs NKB treatment was more likely in inpatient settings [OR=3.73 (3.06-4.55)] and in patients with comorbid congestive heart failure [OR=1.43 (1.12-1.84)].

Conclusions: Clinicians were more likely to treat HK with SZC than SPS or NKB in CKD patients with moderate-to-severe acidosis in a recent large, US, real-world sample. Secondary findings from prior clinical trials suggest that SZC may improve MA as well normalize sK+. Future clinical trials are needed to assess the impact of SZC on sHCO3- concentrations.

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POII133
Real-world RAAS Inhibitor Use and Its Predictors Among Patients Initiating Sodium Zirconium Cyclosilicate
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Background: Renin-angiotensin-aldosterone system inhibitors (RAASI) are associated with reduced risk of death and slower disease progression in patients with heart failure (HF) and chronic kidney disease (CKD). However, RAASI use increases the risk of hyperkalemia (HK), which may disrupt RAASI use and mitigate its benefits. There is limited real-world evidence characterizing RAASI use after sodium zirconium cyclosilicate (SZC) treatment.

Methods: Adult patients initiating SZC (index date) while on a RAASI in outpatient care were included from a large US claims database (January 2018-June 2020). Analyses were conducted among all patients, patients with CKD and patients with CKD + diabetes (DM). The percent of patients with a RAASI prescription at index was summarized. Characteristics among patients with and without a new RAASI fill were compared using descriptive statistics. A multivariable logistic regression model assessed predictors of a new RAASI fill.

Results: A total of 589 patients initiating SZC while on a RAASI were included (mean age 61 years, 65.2% male). Overall, 82.7% of patients had a new RAASI fill after index. The median time to discontinuation was not reached among patients with a new RAASI fill, of whom 88.1% at day 180 and 74.0% at 1 year remained on RAASI therapy. Compared to patients without a new RAASI fill, patients with a new fill had a higher burden of CKD (69.4% vs 58.8%) but a similar prevalence of DM (24.6% vs 28.4%). Results were similar in the CKD cohort (N=398; 84.9% had a new RAASI fill) and CKD and DM cohort (N=311; 85.2% had a new fill). Predictors of having a new RAASI fill included fewer prior hospitalizations (0.77 [0.60-0.98]; p=0.05) and emergency department (ED) visits (0.78 [0.63-0.97]; p=0.05).

Conclusions: In a real-world setting, 83% of patients had a new RAASI fill within 90 days after ending their RAASI. Results are consistent with clinical trial findings and similar among patients with CKD and patients with CKD + DM. Patients with hospital and ED visits will require follow up care to encourage RAASI continuation.

Funding: Commercial Support - AstraZeneca

POII134
Compatibility Study of Patiromer with Juices/Liquids and Soft Foods
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Background: Patiromer is a novel, once-daily, sodium-free K+- binder approved for treatment of hyperkalemia. The drug is a tasteless, odorless powder administered orally to mix patiromer with small amounts (per allowed dietary intake recommendations) of various liquids and foods may improve palatability and medication adherence. This study evaluated the compatibility of patiromer with juices/nectars, soft foods, and other liquids, the mean TKEC at low and high ratios was 8.5–8.7 mmol/g (reference: 9.2 mmol/g); exchange capacity for tested vehicles was within the prespecified range. For all mixtures, compatibility was assessed at two ratio levels: low (8.4 g patiromer in 40 mL of vehicle, ~1/6 cup); high (12.7 g patiromer in 20 mL of vehicle, ~1/4 cup).

Methods: For all mixtures, compatibility was assessed at two ratio levels: low (8.4 g patiromer in 40 mL of vehicle, ~1/6 cup); high (12.7 g patiromer in 20 mL of vehicle, ~1/4 cup; high (12.7 g patiromer in 20 mL of vehicle, ~1/4 cup).

Results: The drug–a tasteless, odorless powder–is administered orally and ED visits will require follow up care to encourage RAASi continuation.

Conclusions: Mixing of patiromer with small amounts of juices/nectars, soft foods, and other liquids, the mean TKEC at low and high ratios was 8.5–8.7 mmol/g (reference: 9.2 mmol/g); exchange capacity for tested vehicles was within the prespecified range. For all mixtures, compatibility was assessed at two ratio levels: low (8.4 g patiromer in 40 mL of vehicle, ~1/6 cup); high (12.7 g patiromer in 20 mL of vehicle, ~1/4 cup).

Commercial Support - AstraZeneca

POII135
Risk of Heart Failure in Patients Who Initiated Sodium Zirconium Cyclosilicate vs. Patiromer
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Background: Hyperkalemia is common in patients with chronic kidney disease (CKD), heart failure, and diabetes. Sodium zirconium cyclosilicate (SZC) and patiromer were recently approved for the treatment of hyperkalemia. Since SZC contains significant amounts of sodium, we assessed the risk of heart failure hospitalization (HHF) associated with the initiation of SZC versus patiromer in non-dialysis patients.

Methods: We used a U.S. commercial insurance claims database (Optum Clínifromatics® Data Mart) between May 2018 (after SZC approval) and September 2020. Participants were non-dialysis adults who had a 180 days of insurance enrollment and were newly prescribed SZC or patiromer. The primary outcome was a hospitalization with a discharge diagnosis of heart failure. The secondary outcome was a hospitalization or an emergency room visit with a diagnosis of any edema. Propensity score (PS) matching in a variable ratio up to 1:3 was used to adjust for more than 80 variables, including demographic characteristics, comorbidities, medication use, and health care utilization. Cox proportional hazards regression models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Our cohort included 1,126 SZC initiators and 2,839 PS-matched patiromer initiators (total N=3,965). The mean age was 72 (±10) years, 30% had a history of heart failure and 85% had CKD stages 3-5. The risk of HHF was higher in the SZC initiators compared to patiromer initiators (HR 1.22, 95%CI 0.95-1.56), but the confidence interval included the null value (Table). Edema was more common in the SZC initiators (HR 1.89, 95%CI 1.05-3.39). In subgroup analyses, initiation of SZC was associated with an increased risk of HHF (HR 1.58, 95%CI 1.01-2.64) amongst patients without a history of heart failure.

Conclusions: Patients initiating SZC may need to monitor volume status and consider dietary salt restrictions and initiation or adjustment of diuretics. Larger studies are needed to more precisely evaluate the safety of SZC in routine practice.

Funding: Commercial Support - AstraZeneca

POII136
RDX013, a Novel, Oral, Small Molecule Being Developed for Treatment of Hyperkalemia, Increases Colonic Secretion and Fecal Excretion of Potassium
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Background: Potassium (K+) homeostasis is maintained by the balance of dietary K+ intake, extra- and intracellular K+ distribution, and renal and intestinal excretion. Hyperkalemia (serum K+>5.0 mM) occurs frequently in CKD patients and can lead to cardiac arrhythmias and sudden death; controlling serum K+ may reduce mortality in this population. Current therapeutic options for the chronic treatment of hyperkalemia are limited to K+-binding agents. Here, we describe the discovery of RDX013, a novel, oral, small molecule K+ secretagogue in development for treatment of hyperkalemia.

Methods: Male Sprague Dawley rats (n=6/group) were orally administered vehicle or 6 mg/kg RDX013 twice daily for 6 days. 24-hour fecal samples collected from rats housed individually in metabolic cages on the final study day were homogenized, and K+ and sodium were analyzed by cation exchange chromatography.

Results: RDX013 significantly increased fecal K+ excretion compared to vehicle control animals (figure). Fecal sodium was also increased by RDX013 (figure), which was expected as luminal sodium retention in the intestine is key to the pharmacodynamic response. Fasting serum potassium was also increased by RDX013 (figure), which was expected as luminal sodium retention in the intestine is key to the pharmacodynamic response.

Conclusions: Based on its unique mechanism of action which involves pharmacologically enhancing K+ secretion through apical K+ channels in the colon, RDX013 is a potential first-in-class therapy which may provide a new approach to managing serum K+ in patients versus commonly prescribed K+ binders. A phase 2 clinical study with RDX013 (NCT04780841) is ongoing in non-dialysis CKD patients with hyperkalemia.

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POI1137

Artificial Intelligence-Assisted Electrocardiography for Early Diagnosis of Thyrotoxic Periodic Paralysis

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Background: Thyrotoxic periodic paralysis (TPP) characterized by acute weakness, hypokalemia and hyperthyroidism is a medical emergency with a great challenge in early diagnosis since most TPP patients do not have overt symptoms. Since both hypokalemia and hyperthyroidism in TPP significantly affect the cardiovascular system, electrocardiography (ECG) as a prompt and non-invasive bedside tool universally used in the ED may detect these electrical changes. To assess artificial intelligence (AI)-assisted electrocardiography (ECG) combined with routine laboratory data in the early diagnosis of TPP.

Methods: A deep learning model (DLM) based on ECG12Net, an 82-layer convolutional neural network, was constructed to detect hypokalemia and hyperthyroidism. The development cohort consisted of 39 ECGs from patients with TPP and 502 ECGs of hypokalemic control; the validation cohort consisted of 11 ECGs of TPP and 36 ECGs of non-TPP with weakness. The AI-ECC based TPP diagnostic process was then consecutively evaluated in 22 male patients with TPP-like features.

Results: In the validation cohort, the DLM-based ECG system detected all cases of hypokalemia in TPP patients with a mean absolute error of 0.26 mEq/L and diagnosed TPP with an area under curve (AUC) of ~0.80%, surpassing the best standard ECG parameter (AUC=0.7285 for the QR interval). Combining the AI predictions with the estimated glomerular filtration rate (eGFR) and serum chloride (Cl) boosted the diagnostic accuracy of the algorithm to AUC 0.960. In the prospective study, our AI ECG system achieved perfect performance (F-measure 100%) on the task of hypokalemia detection in them and the integrated AI with routine laboratory had a PPV of 100% and F-measure 87.5% for TPP diagnosis.

Conclusions: An AI-ECC system reliably identifies hypokalemia in patients with paralysis and its integration with routine blood chemistries provides valuable decision support for the early diagnosis of TPP to avoid life-threatening complication.

POI1138

Will the Real Sodium Stand Up!

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Introduction: Hyponatremia is a common finding as it could be precipitated by multiple factors ranging from medications to simple dehydration. Accurate approach to management depends on assessing serum osmolality in an effort to distinguish cases of true, factitious or pseudohyponatremia. We present a case of hyponatremia secondary to hypothyroidism.

Case Description: 36 year old Asian woman with HTN, Type 2 DM, HLD presented with 1 day of epigastric pain. On exam S1, S2 were heard with vesicular breath sounds throughout, epigastric tenderness and no focal neurological deficits. Initial labs: sodium 114 potassium 3.5 chloride 85 glucose 254, BHB 3.7. Sodium corrected for glucose 116 CO2, BUN, Cr and Ag were calculable. Urinalysis: pH 6.0, ketones < 160, glucose > 1000, protein > 1000. Total cholesterol 1020, HDL 25, Triglycerides >5600, LDL insatiable, serum osmolality 314, lipase 57. Venous blood gas: 7:37/30.194/8.17, sodiometry. VBG 132 Abdominal ultrasound revealed a normal pancreas with hepatic steatosis. She was treated in ICU with normal saline, insulin infusion, isocapent ethyl and gemfibrozil. Abdominal pain resolved and insulin was changed to Glargine. Over three days triglycerides trended down to 1744 and sodium to 132. She was discharged on isocapent ethyl, gemfibrozil, atorvastatin, glargine, metformin and lisinopril, with a sodium of 132.

Discussion: Sodium is most commonly measured by indirect potentiometry (ISE) measurement. By this method serum specimens are diluted based on estimated typical balance of serum to solid blood components. By this method factitious low sodium results are known to occur in patients with significantly elevated lipids and protein. As in this case, direct sodium measured by VBG/ABG are most accurate. Typically markedly elevated serum triglyceride with concentrations > 1500 mg/dl are thought to be responsible for factitious hyponatremia. In our patient the value of serum sodium on admission was unexpectedly low at 114 and severe hyperhypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides measured Na:

\[
\text{Measured Na} = \text{Corrected Na} \times \left(1 \frac{1}{	ext{mg/dL}} \times 1 \frac{1}{	ext{mmol/L}} \times \frac{7.8}{100} \right)
\]

Plasma triglycerides (g/L) x 0.002; measured serum sodium would have been expected to be 125 mEq/L. In cases of extremely high lipids, one must consider lab techniques for measuring serum sodium, as well as full lipid panel in the evaluation and treatment of factitious hyponatremia.

POI1139

Admission Sodium and Related Features to Predict Falls in Machine Learning Models

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Background: Hyponatremia has been associated with an increased risk for falls, but evidence is primarily limited to outpatient events. Hyponatremia is a potential surrogate of conditions that may lead to falling including volume depletion, malignancy, pain, polypharmacy, and weakness. We hypothesized that a model could be developed to predict falls based upon accessible variables present on all hospital admissions. An accurate model could allow for measures to lower in-hospital falls.

Methods: Medical records from a single institution were collected over a period of 2011 to 2019. Subjects included admitted patients who suffered a recorded in-hospital fall and were admitted, and controls matched for admission on the same date. Variables collected included sodium, glucose, age and gender. There were 17,103 patients total of which 1,203 had unique falls. Data was split into an 80% training, 20% validation and 20% testing split. We computed an unadjusted odds ratio of falls for those with very low sodium (<126). We trained logistic regression, random forest, XGBoosted forest, and neural net classifiers. Classifier cutoff was calculated using Youden values.

Results: We did not see an increased incidence of falls in the population with a low sodium (N=377) with an unadjusted odds ratio of 0.62 (CI 0.38-1.01). Similarly, the model performances did not result in clinically useful predictions with a unanimously high false positive and false negative rates (Figure 1).

Conclusions: Despite reports of hyponatremia as an indicator of fall risk we did not observe this. The fall-prediction models did have the capacity for high performance on the training data, but this does not translate to validated performance. This discrepancy is termed ‘overfitting’ and is important to evaluate as machine learning models have a limited capacity than traditional models to incorporate previously seen examples. If a model cannot make predictions on new data it cannot be clinically useful. These models may be enhanced using other basic admission features and is the subject of future work.

POI1140

Association of Serum Sodium Levels with Bone Mineral Density, Fracture, and Mortality in Patients Undergoing Maintenance Hemodialysis

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Background: Hyponatremia is implicated in pathological bone resorption and has been identified as a risk factor for bone fracture in the general population, but limited data exist in patients undergoing dialysis.

Methods: We analyzed a historical cohort of 2,292 patients undergoing maintenance hemodialysis in Japan. We first examined the association of baseline serum sodium levels with metacarpal bone mineral density (BMD) in a subcohort of 456 patients with available data. Next, we examined the association of baseline sodium serum levels with incident fracture and mortality in the overall cohort, using Cox regression models adjusted for potential confounders (age, sex, dialysis vintage, diabetes, prior cardiovascular disease, history of fracture, body mass index, hemoglobin, albumin, and creatinine) and competing risks regression models accounting for death as a competing endpoint.

Results: Baseline mean ± SD serum sodium level in the overall cohort was 139.7 ± 2.9 mEq/L, and among patients with available data, median metacarpal BMD T-score was -2.05 (IQR, -3.35 to -0.99). Serum sodium levels were not associated with metacarpal BMD T-score in unadjusted or adjusted models. During a median follow-up of 5.4 years (IQR, 2.5-7.0 years), 712 patients died; 113 experienced clinical fractures; and 64 experienced asymptomatic vertebral fractures as estimated by height loss. In adjusted Cox regression, serum sodium levels were associated with mortality (HR, 0.95 per 1 mEq/L higher; 95% CI, 0.92-0.98) but not incident clinical fracture (HR, 0.97 per 1 mEq/L higher; 95% CI, 0.90-1.04) or any fracture (a composite of clinical fracture and vertebral fracture). Similar results were obtained in competing risks regression models.

Conclusions: Serum sodium levels were associated with mortality but not BMD or incident fracture in maintenance hemodialysis patients.
PO1141

Hyponatremia, Inflammation, and Hospital Mortality in Hospitalized COVID-19 Patients

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Background: Systemic inflammation has been associated with severe COVID-19 disease. Hyponatremia can result from inflammation due to non-ossimotic stimuli for vasopressin production. Hyponatremia is an independent risk factor for hospital mortality.

Methods: Hospitalized patients with COVID-19 were prospectively evaluated between March and November 2020 at Hospital Posadas in Buenos Aires, Argentina, in order to evaluate the association between hyponatremia and inflammation and its impact on clinical outcomes. Admission biochemistries, high-sensitivity C-reactive protein (hsCRP), ferretin, patient demographics, and outcome data were recorded. Outcomes (within 30 days after symptom) that were evaluated included admission to the ICU during hospitalization, mechanical ventilation, dialysis-requiring AKI, and in-hospital deaths. In-hospital mortality, length of hospital stay (in days), and hospital readmission for any cause within 30 days after discharge were evaluated using comprehensive data from the EHR.

Results: Among 799 hospitalized COVID-19 patients, hyponatremia was present on admission in 366 (45.8%). Hyponatremic patients had higher hsCRP levels than normonatremic patients (median 10.3 [IR 4.8-18.4] mg/dL vs 6.6 [IR 1.6 - 14.0] mg/dL, respectively, p< 0.01), and hsCRP level was inversely correlated with plasma sodium level (Spearman’s correlation coefficient –0.23; p< 0.01). Hyponatremic patients had higher serum ferritin levels than normonatremic patients (median 649 [IQR 492-1168] mg/dL vs 393 [IQR 156-1440] mg/dL, respectively; p< 0.02), and serum ferritin level was inversely correlated with plasma sodium level (Spearman’s correlation coefficient –0.26; p< 0.01). Hyponatremic patients had increased mortality on unadjusted (odds ratio 1.87, 95%CI:1.28-2.73) and adjusted (odds ratio 1.61, 95%CI:1.05-2,49) Cox proportional hazard models. Crude 30-day survival was lower for patients with hyponatremia at admission (mean [SD] survival 22.1 [0.70] days) compared with patients with normonatremia (mean [SD] survival 27.1 [0.40] days, p< 0.01).

Conclusions: This study demonstrates that hyponatremia on admission is common in patients with COVID-19 and is associated with inflammation and in-hospital mortality. Thus, hyponatremia could be a novel marker for identifying patients with COVID-19 at risk for hospital mortality.

PO1142

Trends of Overall Mortality by Severity of Hyponatremia: Five-Year Mortality Rates

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Background: We have previously reported increasing strengths of association between degree of hyponatremia on hospital admission and proportions of overall mortality at 1 year post-hospitalization. It is unclear if this association persists in the long term and if this association with overall mortality occurs in a linear manner. Here, we further explore this association over a longer mean follow up period. We hypothesized that a dose response relationship occurs between varying degrees of hyponatremia and overall mortality.

Methods: We obtained data from 46,783 patients, average age 62.2 years, 51.3% males, admitted from January 1, 2012 to December 31, 2016 at a tertiary referral hospital in Central Wisconsin. Of these, 7468 patients had admitting serum sodium <135 and 39315 controls with normal serum sodium (135-145). We parsed hyponatremia based in varying degrees of hyponatremia compared with controls. We obtained their vital status (alive or deceased) up to December 31, 2018 over a mean follow up period of 4.7 years. We used Cox proportional hazards model to estimate hazard ratios between varying degrees of hyponatremia compared with normonatremia group after adjusting for covariates.

Results: Hyponatremia occurred in 17.9% of total hospitalizations during the study period. Of 7468 patients with hyponatremia, there were 6,135 (82.2%), 995 (13.3%) and 338 (4.5%) with mild, moderate, and profound degrees of hyponatremia respectively. Hazard ratios for mild, moderate and severe hyponatremia when compared to controls were 1.35 (95%CI: 1.26 – 1.43), 1.81 (95% CI: 1.24 – 2.56) and 2.01 (95% CI: 1.24 – 3.27) respectively (all p<0.001) after adjusting for covariates.

Conclusions: All-cause mortality from CVD, stroke, cancer, liver cirrhosis deaths were occurring to a significant proportion even in patients with milder degrees of hyponatremia with a dose response relationship. Clinicians should incorporate hyponatremia in their assessment of critical patients as this is associated with mortality. These findings need to be explored further with research geared towards elucidating mechanisms that contribute to death in hyponatremia, and if correcting sodium levels early in hospitalizations may prevent mortality in the future.

PO1143

The Prognostic Importance of Serum Sodium for Mortality Among Critically Ill Patients Requiring Continuous Renal Replacement Therapy

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Background: Serum sodium derangement is common in critically ill patients requiring continuous renal replacement therapy (CRRT). We aimed to assess the association between serum sodium (normal range 138-142 mmol/L) before and during CRRT with mortality.

Methods: This is a historical cohort study of 1,520 critically ill patients who received CRRT for at least 24 hours from December 2006 through November 2015 in a tertiary hospital in the United States. Using logistic regression analysis, we used serum sodium before CRRT, mean serum sodium, and serum sodium changes during CRRT to predict 90-day mortality after CRRT initiation.

Results: Compared with the normal serum sodium levels, the odds ratio (OR) of 90-day mortality in patients with serum sodium before CRRT of ≥134-147 and ≤148 mmol/L were 1.45 (95% CI 1.03-2.05), 2.24 (95% CI 1.33-3.87), respectively. There was no significant increase in 90-day mortality in serum sodium of ≤137 mmol/L. During CRRT, the mean serum sodium levels of ≤137 (OR 1.41; 95% CI 1.01-1.98) and ≤143 mmol/L (OR 1.52; 95% CI 1.14-2.03) were associated with higher 90-day mortality. The greater serum sodium changes during CRRT were associated with higher 90-mortality (OR 1.35; 95% CI 1.21-1.51 per 5 mmol/L increase).

Conclusions: Before CRRT initiation, hyponatremia and during CRRT, hypo- and hypernatremia were associated with increased mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Restricted cubic spline of the association between serum sodium before CRRT and 90-day mortality

Restricted cubic spline of the association between mean serum sodium during CRRT and 90-day mortality

PO1144

Use of Tolvaptan to Maintain Eunatremia in Acute Brain Injury-Induced SIADH

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Introduction: Hyponatremia is a predictor of in-hospital mortality in intracerebral hemorrhage. In hyponatremia from SIADH, usual therapies may not be ideal in patients with stroke. We present a case of hyponatremia from acute brain injury induced SIADH being managed with Tolvaptan.

Case Description: Our patient is a 68 year old man with a history of hypertension who was admitted for an acute hemorrhagic stroke. He had a blood pressure of 204/127 mmHg over and an NIHSS of 110. His initial work up shows: glucose 199 mg/dL, creatinine 0.75 mg/dL, Na 137 mmol/L, potassium 3.8 mmol/L, HCO3 of 25 mmol/L, chloride 95 mmol/L. A head CT scan demonstrated a 10 cc right thalamic hemorrhage. He was then started on a nicardipine drip. On the next day, he was noted to have a Na of 129 mmol/L. His serum osmolality, urine osmolality, urine Na were 289 mOsm/kg, 6,783 mOsm/kg and 146 mmol/L respectively. He was given salt tablets with...
improvement of Na to 131. However, he developed headaches and became hypertensive at 180/94 mmHg. Instead, he was started on a high protein diet, 1 liter fluid restriction and lasix. The next Na level was 129. He was given Tolvaptan 15 mg, which increased the Na to 132, urine osm 645, and urine Na to 12. The dose was increased to 30 mg to achieve eunatremia with these values: Na 135-138, urine Na 12, urine osm 487. His BP improved, tolvaptan was discontinued and salt tablets were resumed. The patient maintained eunatremia throughout the hospital stay.

Discussion: Hyponatremia is a predictor of mortality due to cellular edema. Eunatremia with Na levels between 135-145 mmol/L is targeted in acute brain injury. SIADH induced by brain injury may be due to an increase in ADH from the overstimulation of the neurohumoral axis. ADH promotes water reabsorption at the cortical and medullary collecting tubules, and inappropriate levels lead to hyponatremia. Tolvaptan is a V2 receptor antagonist which combats this mechanism, thus increasing free water excretion. Additional therapies for hyponatremia from SIADH include fluid restriction, a high protein diet and salt tablets. However, salt tablets increase fluid retention; which increases blood pressure, and leads to recurrent hemorrhage and poor outcomes. The use of Tolvaptan increases free water excretion to achieve eunatremia, thereby decreasing the risk of brain edema and controls blood pressure, especially in this patient population.

PO1145
Acute Severe Symptomatic Hyponatremia in the Post-Partum Period: The Syndrome of Oxytocin-Induced Anti-Diuresis (SOIAD)
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Introduction: Oxytocin (OXT) is a neuropeptide used in pregnancy to induce uterine contraction. It is structurally related to vasopressin (AVP) by a difference of only 2 amino acids. While it does not have antidiuretic activity at physiologic levels, it can when administered at pharmacologic doses (>20 μL/min). We present a case of a severe symptomatic hyponatremia after receiving oxytocin in the post-partum period.

Case Description: A 31 y/o G1P0 woman was admitted with premature membrane rupture at week 38. An IV oxytocin infusion (2μL/min) was started to augment labor. Her serum sNa 6 hrs later was 132 mmol/L (baseline sNa 140). Her delivery was c/v with uterine atony and postpartum hemorrhage requiring a bolus of IV oxytocin (10 U over 30 min) followed by infusion at 8 μL/min. The sNa 18 hr later was 118 mmol/L. She reported nausea. Her sOsm was 252 mOsm/kg with UNa 95 mmol/L and Uosm 880 mosm/kg consistent with the syndrome of anti-diuresis (SIAD). OXT was suspected and was stopped. 2 hr later, a rapid water diuresis ensued (u vol 150-200 m/L, with UNa 92 mosmol/kg). The sNa and 8 hrs later increased to 124 and 127 respectively. Because of concern for over-correction, she was given DDAVP and D5W. This resulted in a gradual (6-8 mosmol/L/24 hr) sNa increase to 140 mmol/L over the next 48 hr (Fig 1).

Discussion: Therapeutic OXT can result in anti-diuresis with water retention. OXT half-life is only 1.6 min and is further reduced during pregnancy. Women are more likely to have severe neurologic sequelae of hyponatremia so it is fortuitous that the half-life of OXT is so short, and discontinuation alone should result in a rapid water diuresis. Still, although acute hyponatremia can usually be safely corrected rapidly, concern over what could have been an increase in sNa of 28 mmol/L over several hrs necessitated a DDAVP clamp to slow correction. She had a complete recovery. SOIAD can be a severe complication of OXT. Since it can occur rapidly and severely, sNa should be followed closely when patients are on OXT infusion.

PO1146
A Rare Cause of Hyponatremia: Renal Salt Wasting Syndrome of Unclear Etiology Post Autologous Hematopoietic Stem Cell Transplant
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Introduction: Hyponatremia is common in cancer patients. We report a rare case of acute hyponatremia in a patient with multiple myeloma (MM) who developed renal salt wasting syndrome (RSWS) as a complication of autologous hematopoietic stem cell transplant (SCT).

Case Description: A 57-year-old female with history of Plasmacytoma treated with radiation therapy that subsequently relapsed as MM with POEMS syndrome and was treated with VRd regimen presented for autologous SCT. MM was in remission and patient underwent Melphalan pre-conditioning with last melphalan dose 48 hours prior to transplant. 36 hours post-transplant patient had a seizure. Labs revealed acute drop in serum sodium from 137 to 117 over 17 hours. CT head revealed mild generalized cerebral edema. Patient also had acute polyuria (> 4 L/day). Patient was treated emergently with hypertonic saline bolus and had resolution of neurological symptoms however, serum sodium continued to drop and she required around 2 L of hypertonic saline infusion over the next 24 hours to correct sodium at desired rate. Urine studies at the time of hyponatremia revealed urine osmolality of 477, sodium 161 and potassium 34. Initial working diagnosis was SIADH that was quickly revised to RSWS based on high urine sodium, hypovolemia and polyuria. The patient was able to be transitioned to salt tablets once polyuria resolved over the next 36 hours. Urine sodium remained elevated. A repeat CT head showed resolution of cerebral edema.

Discussion: RSWS post SCT is rarely reported. Among the few reported cases an underlying CNS complication or a post-transplant hyponatremia inducing medication exposure that predated acute hyponatremia was present. Moreover the reported cases appeared to be non autologous transplants. SIADH and RSWS (including CSWS) are similar in the sense that both present with similar urine studies. Volume status and urine output are the key factors to help differentiate between the two entities. Clinically differentiating between these two entities is important as fluid restriction is the key management in the one and solute plus volume replacement in the other. Based on our case we recommend that hyponatremia post SCT should be carefully evaluated and RSWS be considered in the differential even if there is no obvious underlying cause.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1149

Explainable Prediction of Overcorrection in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial
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Background: Overcorrection of hyponatremia can result in irreversible neurologic disability like osmotic demyelination syndrome. Few prospective studies have identified the individuals at high risk of overcorrection under controlled hypertonic saline treatment.

Methods: We performed a post hoc analysis of a multicenter, prospective randomized controlled study – the SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline In Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia) trial in 178 patients older than 18 years with symptomatic hyponatremia (mean age 73.1 years, mean serum sodium (sNa) concentrations 118.2 mmol/L). Overcorrection was defined as an increase in sNa by > 12/18 mmol/L within 24/48 hours at any time.

Results: Thirty-seven of 178 patients experienced overcorrection (20.7%). Overcorrection was independently associated with initial sNa level (≤ 110 mmol/L: 7 points; 110-115 mmol/L: 4 points; 115-120 mmol/L: 2 points; 120-125 mmol/L: 0 point), chronic alcoholism (7 points), severe symptoms of hyponatremia (3 points), and initial potassium level (< 3.0 mmol/L: 3 points). The NASK score was derived from these four risk factors for overcorrection (hyponatremia, Alcoholism, Severe symptoms, and hypokalemia) and was significantly associated with overcorrection (odds ratio 1.41, 95% CI 1.24 to 1.61; P < .001) with good discrimination (area under the receiver operating characteristic curve 0.76, 95% CI 0.66 to 0.85; P < .001). The AUROC value of the NASK score was statistically better comparing to those of each risk factor.

Conclusions: In treating patients with symptomatic hyponatremia, individuals at high risk of overcorrection were predictable using a novel risk score summarizing baseline information.

PO1148

Cerebral Salt Wasting in a Renal Transplant Patient
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Introduction: Hyponatremia is a common occurrence in patients with cerebral injury and is usually thought to be secondary to SIADH. Though cerebral salt wasting is documented in literature it has been debated on if it is truly a phenomenon. Among patients with CNS disease, CSW is a much less diagnosed cause of hyponatremia and remains underdiagnosed owing to the challenge of proving its existence. Here we present a patient with a CNS injury who showed clear benefit from treatment not centered around SIADH, thus pushing us to diagnose him with CSW.

Case Description: A 63yo Male with a PMHx of DDKT presented with nausea/vomiting. A cerebellar abscess from a previous biopsy site was found and he underwent a debridement and washout. On POD#4 the patient had a drop in sodium to 131. Urine studies [urine osmolarity: 789; urine Na: 72]. With continued drop in sodium and orthostatic hypotension he was started on NS 75cc/hr. The sodium continued to drop to a low of 123. At that time the NS was increased to 125cc/hr. This resulted in an upswing in serum sodium to 130. A drop in NS rate was trialed with sodium dropping back to 127. The NS was eventually ramped up to 200cc/hr with good response. During the uptitration of fluids there was no significant drop in urine osmolality noted. The patient was eventually transitioned to a dose of salt tabs close to the equivalent to the amount of fluids he was receiving [5g Q4H]. He was also started on Fludrocortisone 0.1mg daily. This resulted in our ability to drop the Salt tabs to 4g Q6H with stability in serum sodium noted. He was discharged on this regimen and was noted to have stable serum sodium on follow up a few weeks later.

Discussion: CSW is difficult to diagnose due to the similarities in laboratory diagnostic markers with SIADH. One major difference is that in CSW patients are usually hypovolemic. Another aspect that differs from SIADH is the approach to treatment. In SIADH a combination of fluid restriction, lasix, and salt tabs are used. What makes our case unique is the successful use of NS to correct the patient’s sodium. If this was SIADH, continuous administration of NS would have dropped the sodium level. We believe we met the burden of proof to diagnose this patient with CSW. Though there may still be debate about the existence of CSW, we believe that with the difference in treatment approach it should always be considered in the differential in patients with CNS injury.
Case Description: A 58-year-old male with past medical history of hypertension on amiodpine and losartan presented with nausea, emesis and abdominal pain. The patient was recently discharged 2 weeks earlier s/p uncomplicated distal pancreatectomy with splenectomy for pancreatic adenocarcinoma. Post-operative course was stable with no complications and patient was discharged home on oxycodone/acetaminophen for pain.

At home, the patient noticed constipation with worsening abdominal distension with bilateral lower extremity swelling. He had been oliguric for the past week, performing manual suprapubic compression to void. On readmission patient was noted to be severely dehydrated with a large, distended abdomen. Vital signs were BP 102/53, HR 87, SpO2 97%. Notable labs include (mEq/L): Na 111, BUN 132, Cr 4.4, HCO3 18. Urine studies noted (mEq/L): Na 8, Cl -10, K 25, serum osmolality 366 mOsm/kg. Abdominal CT noted a large LUQ fluid collection, distal colonic distension with focal retention and mild bilateral hydronephrosis. Subsequent foley insertion immediately drained 2.5L. Repeat labs 12 hours later were (mEq/L): Na 118, BUN 118, Cr 2.89. Hypotonic fluids were started to prevent Na overcorrection. Over the next several days the patient’s Serum Na (135) and renal function improved (BUN 21, Cr 0.9) back to baseline.

Discussion: During the post-operative period urinary retention is commonly noted due to anesthesia, analgesics, pain and constipation. This can be exacerbated in elderly male patients due to the ubiquity of BPH. Therefore physicians must be aware of common post-operative complications of urinary retention like hyponatremia, especially given the higher prevalence and predisposition of geriatric populations to develop hyponatremia. The proposed mechanism of urinary retention induced hyponatremia involves bladder distension and/or pain-mediated ADH release.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO1154
Point-of-Care Ultrasound-Assisted Management of Hyponatremia
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Introduction: Point of care ultrasound (POCUS) is emerging as a valuable adjunct to conventional physical examination in patients with complex fluid and electrolyte disorders. Herein, we present a case of hyponatremia where nephrologist-performed focused cardiac ultrasound (FoCUS) aided in accurate diagnosis.

Case Description: A 73-year-old woman was admitted for the treatment of fractures after sustaining a fall. Nephrology was consulted for decrease in serum sodium level (to 123 mmol/L; baseline 130s). Laboratory data was significant for a urine sodium level of 46 mmol/L, urine osmolality 257 mOsm/kg, serum creatinine 0.5 mg/dL and BUN 9 mg/dL. As the patient had exertional dyspnea and crackles at lung bases, IV diuretic was administered by the rounding physician prior to urine studies. No active pain or thiazide use. X-ray showed a huge hiatal hernia with bowel contents in the chest, which was possibly mimicking crackles on auscultation and causing dyspnea. Systolic BP was in 140s. Urine sodium, though suggestive of euvolemic state, was confounded by diuretic. We performed a FoCUS exam. Left ventricular outflow tract velocity time integral (LVOT-VTI), which is a surrogate for stroke volume was lower than expected (~13 cm [normal 18-22]) suggestive of hypovolemia. Flow changes preceded drop in BP. We recommended to administer normal saline and the serum sodium improved to 130 mmol/L in 2 days; VTI normalized to ~22 cm [Fig. 1].Fig.2 illustrates stroke volume estimation using LVOT diameter and VTI. As the diameter is constant for a given person, VTI alone can be used to monitor response to therapy.

Discussion: POCUS is a valuable bedside diagnostic tool in day-to-day nephrology practice.

PO1156
Identifying Hypernatremia Subgroups with Differing Survival by Machine Learning Among Hospitalized Patients
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Background: The objective of this study was to characterize patients with hypernatremia on hospital admission into clusters using an unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

Methods: We performed consensus cluster analysis based on demographic information, principal diagnoses, comorbidities, and laboratory data among 6,297 hospitalized adult patients with hypernatremia present at admission. We calculated the standardized difference of each variable to identify each cluster’s key features. We assessed the association with each hypernatremia cluster with in-hospital and one-year mortality.

Results: There were three distinct clusters of hypernatremia: 1,570 patients (25%) in cluster 1; 2,648 (42%) in cluster 2; and 2,079 (33%) in cluster 3. Figure 1 is a plot of standardized mean differences to visualize key features for each cluster. Compared to cluster 2, the odds ratios for in-hospital mortality were 6.99 (95% CI 4.03-12.13) for cluster 1 and 5.73 (95% CI 3.31-9.90) for cluster 3, whereas hazard ratios for one-year mortality were 3.38 (95% CI 2.69-4.25) for cluster 1 and 4.71 (95% CI 3.82-5.80) for cluster 3.

Conclusions: The characteristics and outcomes of hospitalized patients admitted with hypernatremia were heterogeneous. Our cluster analysis identified three clinically distinct phenotypes with differing mortality risks. Identification of heterogeneity in hypernatremic patients using this approach may provide guidance for the management of hospitalized patients with hypernatremia at the time of hospital admission.

PO1155
Polyethylene Glycol-Induced Pseudohyponatremia
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Introduction: Pseudohyponatremia due to Polyethylene glycol (PEG) is poorly described and goes unrecognized. We describe a case of hyperosmolar pseudohyponatremia due to PEG absorption into the systemic circulation.

Case Description: An 84-year-old lady with hypertension and CKD stage 4 was admitted with an asymptomatic serum sodium of 121. Initially thought to be due to SIADH. She was started on 1-liter fluid restriction, sodium chloride tablet and torsemide. Nephrology was consulted on day 3 as her serum creatinine was 2.9 (baseline 2.3 mg/dl) and sodium improved to only 124. Patient complained of increased thirst and had dry mucus membrane on examination. Labs on admission revealed a serum sodium of 121 mEq/L, a serum osmolality of 286 mOsm/kg, urine osmolality of 230 mOsm/kg and urine sodium of 40. Serum creatinine was 2.3 mg/dL, BUN 50 mg/dL, glucose of 100mg/dL, uric acid 8.1 mg/dL. Thyroid function tests and cortisol were within normal range. An osmolar gap of 22 was noted. In the absence of hyperglycemia and other potential causes of an osmotic gap, such as mannitol or alcohol, a careful review of medication showed that she was on 3 weeks of PEG for constipation. PEG was held, fluid restriction and torsemide discontinued. Resolution of osmolar gap was confirmed in two weeks with return in sodium to 134 and creatinine to 2.3.

Discussion: The prevalence of hyponatremia is reported at 7% in bowel prep patients. Etiology in these cases was due to increased free water intake. Hyperosmolar hyponatremia is caused by the addition of an ‘effective solute’ (e.g. glucose, mannitol or sucrose) to the serum. Commonly used as an osmotic laxative, PEG is described as ‘a nonabsorbable, nonmetabolized polymers’ that when administered orally acts as a ‘pure osmotic agent’ in the gastrointestinal tract. Systemic absorption can occur in rare cases. When PEG absorption occurs, most of its clearance occurs via renal filtration, this process is likely impaired in a patient with CKD such as seen in our patient. When a patient presents with hyponatremia, the expectation of a low-serum osmolality needs to be confirmed with the actual measurement of serum osmolality. This case highlights the importance of detecting the etiology of hyponatremia without which treatment of the same can be impossible and expands the understanding of normal to high serum osmolality can go beyond the commonly known mannitol, paraproteinemia and lipidemia.
**PO1157**

A Rare Case of Acute Myeloid Leukemia Presenting as Central Diabetes Insipidus

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**Introduction:** Central Diabetes Insipidus (CDI) is an uncommon condition, with an overall incidence of approximately 1:25,000 and is usually associated with neurosurgery, trauma, and vascular disease, infiltrative disorders, hypoxic brain injury, and head trauma. Patients with acute myeloid leukemia (AML) mostly present with symptoms of pancytopenia, not hematologic abnormalities and are subsequently diagnosed with AML after bone marrow biopsy. Here we describe a unique case of a patient who presented with symptoms of CDI and incidentally diagnosed with AML.

**Case Description:** A 64-year-old male with a history of coronary artery disease presented to his primary physician complaining of polyuria and polydipsia which affected his work as a truck driver. Labs were notable for mild anemia (Hgb 11 g/dL) with macrocytosis, anemia, and thrombocytopenia (platelet 667 K/uL), serum sodium was 146 mEq/L, Hgb Alc 5%, prostatic-specific-antigen 1.4 ng/mL, normal lipids panel, and normal thyroid function. No definitive diagnosis was made and he underwent evaluation by hematology. Peripheral smear showed increased (44%) blasts/promyelocytes, consistent with acute leukemia. Cytogenetic analysis showed an abnormal clone of cells with an inverted chromosome 3 and monosomy for chromosome 7. He was admitted for induction therapy and presenting symptoms worsened (~1 L urine output per day) along with hypernatremia which peaked at 160 mEq/L, serum osmolality 319 mOsm/kg and urine osmolality and serum osmolality and urine osmolality.

**Discussion:** The presentation of AML with concurrent CDI is associated with chromosome 3 or 7 abnormalities, not brain lesions, as in this case; the management of CDI involves continued DDAVP administration. Unfortunately this translocation has been associated with poorly differentiated acute myeloid leukemia. With this case, we suggest screening patients with CDI for who have an unclear reason of developing hypernatremia which peaked at 160 mmol/L, serum osmolality 319 mOsm/kg and urine osmolality.

**Conclusion:** This case reinforces the association between ketamine and central DI related to ketamine. We present a unique case of central DI associated with ketamine injection in a critically ill patient with acute respiratory failure.

**Case Description:** A 52-year-old African American man with a medical history of bipolar disorder, polysubstance abuse, chronic obstructive pulmonary disease, hypertension, and deep vein thrombosis was admitted to the medical intensive care unit with hemoptysis and acute respiratory failure. Due to agitation and refractory hypoxemia he required multiple sedating agents. Within hours of starting a ketamine infusion his urine output increased from a mean of 71 mL/hr to 305 mL/hr. Over 48 hours serum sodium (Na+) rose from 142 to 159 mM/L. Urine osmolality (Uosm) was 132 Osm/kg, 4 mcg intravenous (IV) desmopressin was administered. 90 minutes later Uosm had increased to 646 Osm/kg. Urine output fell to 49 mL/hr. About 28 hours after the initial dose of desmopressin polyuria recurred and Uosm fell to 272 Osm/kg. IV desmopressin was re-administered at 2 mcg with a similar response to the first dose. Sodium normalized with free water replacement. Ketamine was stopped. Urine output, Uosm, and Na+ remained stable without further intervention. Alternative etiologies for central DI such as hypoxic brain injury were considered but felt to be less likely due to the strong temporal relationship with ketamine. The Naranjo adverse drug reaction (ADR) likelihood score was 5 indicating a probable ADR.

**Discussion:** This case reinforces the association between ketamine and central DI which has been described in prior case reports. A hypothesized mechanism is ketamine’s antagonism of N-methyl-D-aspartate receptors in the posterior pituitary thus inhibiting arginine vasopressin production. Ketamine is being used with greater frequency in critical care. In these cases it is important to recognize this rare but potentially serious complication. Monitoring of Na+, Uosm, and urine output should be considered. When central DI related to ketamine is identified, withdrawal of the drug appears to be corrective.

**PO1158**

A Case of Ketamine-Induced Diabetes Insipidus

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**Introduction:** To our knowledge there have been six previously published case reports describing central diabetes insipidus (CDI) related to ketamine. We present a unique case of central DI associated with ketamine injection in a critically ill patient with acute respiratory failure.

**Case Description:** A 62-year-old female with no known past medical history with a history of smoking and 2+ gestations of her second pregnancy. Workup was significant for elevated creatinine with proteinuria and pyuria, normal anion gap metabolic acidosis, hypokalemia, and hyponatremia. Urine studies revealed an inappropriately alkaline urine with impaired renal reclamation of potassium and phosphorus. Serological workup was significant for positive ANA, SSA, and SSB antibodies. Kidney biopsy revealed acute tubulointerstitial nephritis. The patient was started on an IV steroid course with oral tapav and hydrochloroquine with improvement in Cr from 2.2 to 1.2 mg/dL with a potassium, phosphate and sodium bicarbonate supplementation regimen.

**Discussion:** Sjogren’s syndrome is typically associated with lymphocytic infiltration of exocrine glands. However, this can also affect the kidneys causing tubulointerstitial nephritis and defects in tubular function initiating a cascade of electrolyte abnormalities. Understanding the renal physiology behind the observed electrolyte abnormalities is important to optimize our treatment regimen. While the management of a distant ATA has been well described in Sjogren's syndrome typically involves judicious potassium and alkali supplementation, this case highlights the worsening potassium wasting and phosphorous wasting which also needs to be addressed with a concomitant proximal tubulopathy. We propose that this set of features can best be explained by dysfunctional acid-base axis, a cause of the extremely rare type III RTA. We use this case presentation to highlight the spectrum of renal manifestations of Sjogren’s syndrome and their treatment principles.

**PO1161**

Evidence for Abnormal Linkage Between Urine Oxalate and Citrate Excretion in Human Kidney Stone Formers

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**Background:** Animal models have demonstrated an interactive relationship between the epithelial anion exchanger SLC26A6 and carbonate, a cause of the extremely rare type Ia RTA. This relationship is a potential mechanism to protect against kidney stones as higher urine oxalate is accompanied by higher urine citrate but it has not been explored in humans.

**Methods:** We examined 24-hour urine data on 13,155 kidney stone forming patients (SF) from separate datasets at the University of Chicago and Litholith, a national laboratory, and 143 non-kidney stone forming participants (NSF) to examine this relationship in humans. We used autoregressive linear regression models to examine the association between oxalate and citrate in all study participants and separately in SF and NSF.

**Results:** Higher urinary oxalate was associated with higher urinary citrate in both SF and NSF. In NSF, the multivariate adjusted urinary citrate excretion was 3.0 (1.5 to 4.6) (mmol)/creatinine (mmol) per oxalate (mmol)/creatinine (mmol). In SF, the multivariate adjusted urinary citrate excretion was 0.3 (0.2 to 0.4) (mmol)/creatinine (mmol) per oxalate (mmol)/creatinine (mmol).

**Conclusion:** This case highlights the worsening potassium wasting and phosphorous wasting which also needs to be addressed with a concomitant proximal tubulopathy. We propose that this set of features can best be explained by dysfunctional acid-base axis, a cause of the extremely rare type III RTA. We use this case presentation to highlight the spectrum of renal manifestations of Sjogren’s syndrome and their treatment principles.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

380
PO1162
Higher Risk of Incident Kidney Stones in Patients with Metabolic Acidosis and CKD
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Background: Epidemiological studies have shown an association between kidney stones and risk for CKD and its progression. Some types of stones are less likely to form at higher urine pH. Metabolic acidosis is a risk factor for CKD progression, but the association of serum bicarbonate with risk of incident kidney stones is not well understood.

Methods: Optum’s de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with data a 3 years pre-index. The first qualifying serum bicarbonate test established the index date. Primary exposure variables were baseline serum bicarbonate and change in serum bicarbonate over time. Adjusted time-dependent Cox Proportional Hazards models were performed to evaluate time to first occurrence of kidney stones (by ICD-9 or ICD-10 diagnosis codes) during an average 3.6 year follow-up period. Other covariates included age, sex, race-ethnicity, and income status, history of kidney stones, pre-index comorbidities associated with kidney stones, bariatric surgery, obesity, smoking history, baseline eGFR.

Results: 142,904 patients qualified for the study cohort. Patients with metabolic acidosis at index experienced kidney stones at greater frequency than those with normal serum bicarbonate: 19% vs 9%, p<0.0001. Other significant factors associated with incident kidney stones included male sex, history of kidney stones, hyperoxaluria, and osteoporosis. Both higher serum bicarbonate at baseline (HR 0.956, 95% CI: 0.948-0.964) and higher serum bicarbonate over time (HR 0.968, 95% CI: 0.961-0.974) were associated with reduced risk of kidney stone development. The observed associations were unchanged in analyses examining death as a competing risk.

Conclusions: In patients with CKD, metabolic acidosis (vs. normal serum bicarbonate) was associated with a higher incidence of kidney stones and shorter time to incident stone formation. Future investigations should evaluate these associations by stone type.

Funding: Commercial Support - Tricida, Inc.

PO1163
The Association of Body Mass Index with the Development of Metabolic Acidosis in Patients with CKD
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Background: Bone is the largest body fluid and body mass index (BMI) is directly related to bone mass. We explored the relationship between BMI and incident metabolic acidosis in patients with CKD.

Methods: Optum’s de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values in the normal range (22 to <30 mEq/L) or metabolic acidosis (22 to <12 mEq/L normal serum bicarbonate) with data a 3 years pre-index. The first qualifying serum bicarbonate test established the index date. Primary exposure variables were baseline serum bicarbonate and change in serum bicarbonate over time. Adjusted Cox Proportional Hazards models were performed to evaluate the time to development of new-onset metabolic acidosis (serum bicarbonate 12 to <22 mEq/L) over a follow-up period of ≥11.5 years. Other covariates included age, sex, race, education and income status, diabetes or heart failure, eGFR, loguricemia to-calcium ratio, albuminuria, and serum creatinine. Multivariate Cox regression analysis was performed using independent variables (BMI, serum bicarbonate, change in serum bicarbonate, loguricemia to-calcium ratio, albuminuria, and serum creatinine).

Results: 97,294 patients qualified for this study. There was an inverse association between BMI category and the risk of developing metabolic acidosis. Compared to BMI category of 18.5-25, each incremental category of higher BMI was associated with a decreasing risk of developing metabolic acidosis: BMI 25 to <30, HR 0.866, 95% CI: 0.824-0.911; BMI 30 to <35, HR 0.770, 95% CI: 0.729-0.813; BMI 35 to <40, HR 0.664, 95% CI: 0.622-0.709; BMI 40+; HR 0.612, 95% CI: 0.571-0.655. Additionally, hypocalciuria and decreased HDL cholesterol and elevated triglycerides increased the risk of new-onset metabolic acidosis.

Conclusions: In this large cohort of patients with CKD, an incremental increase in BMI was inversely associated with the development metabolic acidosis. The mechanism of this association merits further study.

Funding: Commercial Support - Tricida, Inc.

PO1164
Effects of Pseudohyponatremia on the Diagnosis of Severe Metabolic Acidosis
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Introduction: Pseudohyponatremia is defined as falsely low sodium levels in plasma caused by severe hyperlipidemia or hyperproteinemia. We discuss a case of pseudohyponatremia due to hypertriglyceridemia in a patient admitted with severe metabolic acidosis and acetaminophen induced liver toxicity.

Case Description: 43-year-old male with hyperlipidemia, diabetes mellitus, and obesity presented with 4 day history of abdominal pain, nausea, vomiting, and polydipsia. He had decreased intake and was not taking his insulin for 4 days. Medications include glargine insulin, dulaglutide, empagliflozin, lisinopril, furosemide and losartan. BP:141/59 mmHg, HR:125 bpm, respirations 28/min, Temperature: 98.7, SpO2. 95% on room air. He appeared clinically volume depleted. Laboratory testing revealed severely lipemic serum, elevated acetaminophen level 44.1 ug/ml, severely elevated transaminases, arterial pH: 7.03, pCO2 11 mmHg, HCO3~ <5 mEq/L. Plasma sodium:109 mEq/L and chloride 81 mEq/L using indirect potentiometry and 131 and 111 mEq/L using direct potentiometry. Serum triglycerides 2951 mg/dl, blood glucose 204 mg/dl, plasma lactate 7.5 mmol/L, and creatinine 0.6 mg/dl. Plasma anion gap was 11 mEq/L using direct potentiometry and could not be calculated using indirect potentiometry, as bicarbonate concentration could not be determined due to lipemia. Based on severe metabolic acidosis, elevated lactate, and positive urinary ketones, a diagnosis of lactic acidosis and suspected euglycemic DKA was made. Patient was treated with DKA-protocol with insulin and fluid resuscitation, and N- acetylcysteine for acetaminophen induced liver toxicity. Metabolic acidosis markedly improved over the next 72 hours. Hypertriglyceridemia, transaminase elevations, and metabolic acidosis fully resolved during 6 week follow up visit.

Discussion: Severe hyperlipidemia reduces water content of plasma such that autoanalyzers utilizing indirect potentiometry requiring sample dilution, result in pseudohyponatremia. Direct potentiometry does not require sample dilution and measures true sodium concentration, however, plasma anion gap is reduced due to higher measured chloride concentrations with direct potentiometry. Therefore, physicians must be familiar with the laboratory methods to correctly interpret the plasma anion gap in management of metabolic acidosis when using direct potentiometry measurements.

PO1165
Anion Gap Metabolic Acidosis on Continuous Renal Replacement Therapy: Are You Missing Something?
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Introduction: Anion gap metabolic acidosis is a common metabolic abnormality seen in the clinical practice. Causes includes Lactic acidosis, Ketoacidosis, Renal failure, volatile acid toxicity and salicylate poisoning. Ketoacidosis is due to decreased glucose and insulin availability leading to starvation ketosis and diabetic ketoacidosis respectively. Ketoacidosis is uncommonly seen in patients on prolonged continuous renal replacement therapy. We present 2 cases at Grady Hospital admitted with Acute hypoxic Respiratory Failure due to COVID 19 pneumonia, developed euglycemic ketoacidosis on Continuous Renal Replacement Therapy.

Case Description: case 1: 73 male with the history of HTN, DM, CKD III admitted for acute hypoxic respiratory failure due to COVID 19 pneumonia. He was intubated on admission day 9. Course got complicated by hypotension during intubation leading to Acute Renal Failure on day 11. Patient was started on Renal Replacement Therapy on day 12 due to volume overload and acidosis. Day 19, Anion gap worsened and beta hydroxybutyrate was elevated. Patient was started on insulin drip with resolution of acidosis on day 20. Case 2: 48 yo male with the history of HTN, DM II, CKD stage III admitted for Altered mental status, hypotensive emergency and cough. He was diagnosed with COVID 19 Pneumonia. Patient had non obstructive acute kidney injury on admission. Hospital day 11, patient was oliguric, volume overloaded and hyperkalemia prompted Renal replacement therapy initiation. Day 14, Anion gap worsened and beta hydroxybutyrate was elevated. Tube feed were initiated and Dihydate prescription was continued leading to resolution of anion gap on day 12.

Discussion: Diabetic ketoacidosis is a medical emergency commonly in patients with Type 1 DM but also in Type II DM patients as well. It occurs due to decreased insulin concentration or increase insulin resistance with or without decreased glucose availability leading to release of counterregulatory hormone and fatty acid metabolism producing ketocids. Diagnostic criteria include pH<7.3, Serum HCO3<18, Serum glucose>250mg/dl and positive urine ketones. Euglycemic DKA is a subtype of DKA with serum glucose<200 mg/dl. Incidence of Euglycemic DKA varies from 2-6.3%. Continuous renal replacement therapy is an under-recognized cause of Euglycemic DKA in patients with Diabetes Mellitus.
PO1166
A Wide-Awake Patient with Severe Hypoglycemia and Lactic Acidosis
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Introduction: Severe hypoglycemia is associated with altered mental status or loss of consciousness. We report an intriguing patient who had advanced liver disease and presented with severe hypoglycemia and lactic acidosis without any alteration in mental status.
Case Description: 57-year-old female with severe decompensated alcoholic liver cirrhosis, ascites and recurrent hepatic hydrothorax presented to the Emergency Room with worsening shortness of breath. She had poor oral intake except for actively consuming ethanol. Chest X ray revealed worsening right hydrothorax. Routine blood tests revealed severe hypoglycemia (serum glucose 28mg/dL, severe anion gap metabolic acidosis (arterial pH 7.11, serum bicarbonate 6mmol/L, anion gap 40 mmol/L) and acute kidney injury with elevation of serum creatinine to 2.2 mg/dL. Subsequent laboratory investigations revealed serum lactate level of 23mmol/L. Serum ethylene glycol, methanol, salicylate and acetaminophen levels were undetectable. She had no seizures, malignancy or hypoxia. The patient was alert and oriented. She was hemodynamically stable. There was no evidence of sepsis, tissue hypoperfusion or bowel ischemia. She was not taking any medications which may have led to hypoglycemia or lactic acidosis. The patient was administered intravenous glucose with rapid improvement of her serum glucose and lactate level.
Discussion: This patient had no alteration in mental status despite severe hypoglycemia. Under normal circumstances, the brain primarily depends on glucose as the primary fuel. Studies have shown that under conditions of hypoglycemia and elevated serum lactic acid levels, lactate may serve as an alternative source of energy for the brain. We hypothesize that hyperlactatemia, by providing an alternate energy source, prevented mental status changes in this patient with severe hypoglycemia. Correction of hypoglycemia led to rapid correction of hyperlactatemia suggesting that perhaps lack of glucose may have contributed to hyperlactatemia. We did not identify any obvious cause of hypoglycemia or hyperlactatemia except for her end stage liver disease, continued ethanol use and perhaps her oliguric acute kidney injury. This patient illustrates that hyperlactatemia may be neuroprotective in severely hypoglycemic patients.

PO1167
Sleeping Beauty: Hypersomnolence and Hyperammonemia in a Patient with Multifocal Myeloma
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Introduction: Metabolic encephalopathy in a patient with multiple myeloma is commonly reported in association with prevalent biochemical syndromes such as uremia, hypercalcemia, and or hyperviscosity due to immunoglobulin, but very rarely hyperammonemia has been described as another cause of encephalopathy.
Case Description: The patient is a 45 year old woman with a prior diagnosis of multiple myeloma in July 2020. A bone marrow biopsy confirmed plasma cell neoplasm with 90% plasma cells, and SPEP was positive for monoclonal IgA kappa. The patient was brought to the hospital again in August 2020, with the chief complaint of worsening confusion and hypersomnolence over two weeks. Labs included hemoglobin 7.3 g/dL, serum calcium 13.8 mg/dL, chloride 108 mEq/L, bicarbonate 16 mEq/L with anion gap of 19, lactate 1.4 mmol/L, albumin 3.2 g/dL, and a CT of the head showed numerous lytic skull lesions, including a 3.8 cm posterior skull lesion with extraosseous intracranial extension. The patient was transferred to Methodist Hospital, where a bone-marrow biopsy revealed 19% plasma cells, and SPEP was positive for monoclonal IgA kappa. The patient was administered intravenous glucose with rapid improvement of her serum glucose and lactate level.
Discussion: This patient had no alteration in mental status despite severe hypoglycemia. Under normal circumstances, the brain primarily depends on glucose as the primary fuel. Studies have shown that under conditions of hypoglycemia and elevated serum lactic acid levels, lactate may serve as an alternative source of energy for the brain. We hypothesize that hyperlactatemia, by providing an alternate energy source, prevented mental status changes in this patient with severe hypoglycemia. Correction of hypoglycemia led to rapid correction of hyperlactatemia suggesting that perhaps lack of glucose may have contributed to hyperlactatemia. We did not identify any obvious cause of hypoglycemia or hyperlactatemia except for her end stage liver disease, continued ethanol use and perhaps her oliguric acute kidney injury. This patient illustrates that hyperlactatemia may be neuroprotective in severely hypoglycemic patients.

PO1168
Renal Outcomes and Safety Profile of Direct Peritoneal Resuscitation (DPR)
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Background: DPR is a novel technique used after damage control surgery where peritoneal dialysis fluid is continuously irrigated and drained from the peritoneal cavity in a open abdomen. This has been shown to improve intestinal perfusion, leading to faster abdominal closure. We analyzed the safety profile in terms of changes in the electrolyte profile.

PO1169
Pyroglyutamic Acidosis: Gaps in the Gaps
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Introduction: Prolonged use of acetaminophen can lead to an acquired form of pyroglyutamic acidosis, a form of anion gap metabolic acidosis (AGMA) from increased production of 5- Oxopropionate (pyroglyutamic acid). 5- Oxopropionate accumulates in the body due to the failure its breakdown by 5- Oxopropionilase and is excreted in urine causing positive anion gap (AG).
Case Description: Case 1: First patient is a 59 y/o man with normal prior renal function with baseline creatinine (Cr) of 0.7mg/dL admitted with severe pancreatitis. At the time of presentation his serum calcium level 15mg/dL (8.5-10.5) and his serum Cr level was 2.21 mg/dL. His hospital course was complicated by sepsis due to multiple intra-abdominal infections and required iv pressor and ventilator support. He was later started on continuous veno-venous hemofiltration (CVVH) temporarily with recovery of renal function. Acetaminophen 1 gram three times daily was administered for pain control. On the 65th day of hospitalization, his bicarb was 15 with an AG of 14, but when corrected for low albumin of 1.8, it increased to 20. HE had a positive urine AG and his urine 5-Oxopropionate was 1583 mmol/mol Cr (range <62).
Results: Case 2: Second case is a 74-year-old man with a history of stage 4 CKD admitted with sepsis due to perforated viscus. He had long hospital course due to ischemic gut with continued bleeding and sepsis due to perforation. He was on Acetaminophen 1 gram four times daily for pain control. His serum bicarbonate started trending down to a nadir of 11 mmol/L on the 43rd day of admission. He had an anion gap of 12, but corrected anion gap was 18 and had a positive urine AG. His urine 5- Oxopropionate was 6316 mmol/mol creatinine (range <62).
Discussion: Both patients in our case series had critical illness, were malnourished, and was recovering from prolonged infection and sepsis which are risk factors for pyroglyutamic acidosis and low serum albumin levels. Their AG might appear to be within normal range if not corrected for albumin. Urine anion gap is an indirect method of measuring urine ammonia excretion is and is elevated in renal tubular acidosis and from excretion of organic anions like 5-Oxopropionate and ketone bodies. Correction for AG is proposed as measured AG + 2.5x (“normal” albumin –4.2 – measured albumin [g/dL]). This equation is called “normal AG” with a positive urine AG due to pyroglyutamic acidosis can mimic renal tubal acidosis and can be easily missed.
**PO1170**

**Diffuse Large B Cell Lymphoma and Synchronous Colon Adenocarcinoma Presenting with Type B Lactic Acidosis Secondary to the Warburg Effect in a Hispanic Man**

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**Introduction:** Lactic acidosis is a major metabolic dysregulation characterized by hyperlactatemia and acidemia that is commonly associated with tissue hypoperfusion. In very rare circumstances, hematological malignancies have been associated with a paraneoplastic syndrome characterized by the modification of the metabolism of cancerous cells from aerobic to anaerobic glycolysis.

**Case Description:** A 61-year-old man presented to the hospital due to generalized body weakness. He was recently admitted to the hospital due to left knee pain; at that time incision, drainage, and tissue sample were done. The patient was discharged home with wound care and antibiotics. On presentation, patient was found to be tachypneic, hypotensive with Kussmaul breathing. A warm erythematous lesion was seen on left lower extremity. Laboratory results showed WBC 20,000/mm³, Hemoglobin 10 g/dL, Platelets 340 × 10³/mm³, creatinine 7.9 mg/dL, Bicarbonate 5 mmol/L, Lactate 6.21 mg/dL, and Ferritin 326 mg/dL, blood cultures positive for Enterobacter. Broad-spectrum antibiotics were administered. Nephrology consultation and dialysis started emergently. The pathology report showed Diffuse Large B-Cell Lymphoma. During the hospital stay, patient acidosis was persistent despite adequate renal replacement therapy and resolution of the septic process. ABG was done showing serum pH of 7.2, Bicarbonate 9 mmol/L, Lactic acid 17.5 mg/dL. Bowel ischemia was ruled out with CT angiogram however imaging showed neoplastic infiltration of peritoneal abdominal structures associated with multiple small nodules. Colonoscopy demonstrated synchronous colon adenocarcinoma. The decision was made to treat the patient with chemotherapy. One week after chemotherapy lactic acid trended down to 1.1 mg/L. The metabolic acidosis and renal function improved and RRT was stopped.

**Discussion:** Usually, lactic acidosis is a sign of hypoperfusion and septic shock. In this case, the source of lactic acidosis was not hypoperfusion but rather a rare paraneoplastic syndrome that leads to anaerobic metabolism of malignant cells, known as the Warburg effect. This condition can be fatal. Prompt initiation of chemotherapy is recommended.

**PO1171**

**Distal Renal Tubular Acidosis in Patients with Autoimmune Diseases**

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**Background:** Distal renal tubular acidosis (DRTA) is reported in association with autoimmune diseases. DRTA can evolve without symptoms and systemic acidosis, this form being defined as incomplete DRTA. The incomplete form necessitates the use of a urinary acidification test like the Furosemide and Fludrocortisone test for establishing the diagnosis.

**Methods:** We conducted a prospective observational study in a selected cohort of 48 patients diagnosed with autoimmune diseases (SLE,SJögren syndrome, ANCA vasculitis, cryoglobulinemic vasculitis), who presented in our clinic from December, 2020 until May, 2021. The patients were submitted to Furosemide and Fludrocortisone test for establishing the diagnosis.

**Results:** The study included 48 patients (36 females, mean age 41.92 ± 15.7 years), diagnosed with SLE (33 patients), pANCA vasculitis (7 patients), cANCA vasculitis (1 patient), SJögren syndrome (3 patients) and cryoglobulinemic vasculitis (4 patients). There was a significant difference regarding age (p=0.001) and eGFR (p=0.001) between the groups with vasculitis (mean age 60.75±23.3 years; eGFR 41.66 ± 16.71 ml/min/1.73 m²), SLE (mean age 35.18 ± 11.74 years; eGFR 73.24 ± 25.18 ml/min/1.73 m²) and SJögren syndrome (mean age 40.05 ± 20.03 years; eGFR 35.56 ± 17.24 ml/min/1.73 m²). The test was positive for 11 patients out of 48. There was not a significant change in inemia during the test (p=0.806). There was a significant increase in the level of serum bicarbonate (26.23 ± 3.5 mmol/l before the test vs 28.21 ± 1.3 mmol/l after the test, p=0.001) and also in the level of serum pH (7.36 ± 0.43 before the test vs 7.45 ± 0.43 after the test, p=0.001). None of the patients reported digestive or allergic side effects. There was not a significant difference regarding eGFR (p=0.665), proteinuria (p=0.372) and CRP (p=0.246) between the patients with or without a positive test. Regarding immunological activity, patients with a positive test had a higher ANA value at the meanement of the test (4.71 ± 3.04 U/ml vs 2.50 ± 2.55 U/ml, p=0.05) and a lower C4 value (12.66 ± 9.39 mg/dl vs 23.4 ± 11.54 mg/dl, p=0.016).

**Conclusions:** Incomplete DRTA was found in 11 out of 48 patients with autoimmune diseases. None of the patients developed severe hypokalemia or metabolic alkalosis or any other side effect after Furosemide and Fludrocortisone test.
A Patient with Combined Metformin-Induced Lactic Acidosis and Euglycemic Diabetic Ketoacidosis

Introduction: Metformin is a small, non-protein-bound molecule that can cause lactic acidosis in 6 out of 100,000 patients with a mortality rate of 30-50%. Concurrent euglycemic diabetic ketoacidosis (DKA) from sodium-glucose co-transporter-2 (SGLT2) inhibitor has been reported in one case. We report a unique case of a patient with acute kidney injury (AKI) in the setting of metformin-induced lactic acidosis and osmotic diuresis due to euglycemic DKA complicated by celexocib use.

Case Description: A 66-year-old female with a past medical history of type 2 diabetes mellitus for 21 years on metformin 1000 mg twice daily and empagliflozin 25 mg daily with baseline eGFR 51 mL/min/1.73m² 5 months prior, who was also on celexocib 200 mg daily for 40 days presented for elective cervical discectomy which was canceled due to AKI. On exam, blood pressure was 119/59 mmHg, pulse was 92 beats/min, and the temperature was 36.1°C. She was tachypneic at 24 breath/min. Labs showed sodium 136 mg/dL, potassium 8.4 mg/dL, bicarbonate 9 mg/dL, BUN 83 mg/dL, creatinine 8.78 mg/dL, and glucose 117 g/dL. Lactic acid was 3.8 mmol/L after 24 hours. Creatinine improved to 2.46 mg/dL on day 4 without further intervention. She was discharged off metformin, empagliflozin, and celexocib.

Discussion: Metformin is readily dialyzable but has a large volume of distribution. There is no specific antidote available to reverse the toxic effects of metformin or consensus on the modality of renal replacement therapy. Previously demonstrated biphasic elimination pattern of metformin intoxication suggests that a brief HD session is not sufficient to eliminate metformin due to a rebound phenomenon, but it is essential to correct severe acidosis and electrolyte derangements. Hyperkalemia required the use of HD which needed to be followed by CKRT as a more physiological way to maximize the correction of severe acidosis and electrolyte derangements.

Explaination of the high AG: The Figure describes the calculation of AG. In this patient, phosphate was a major contributor to the AG.

PO1176

Is an Increase in Anion Gap a Predictor of Hemodialysis Initiation in Patients with Advanced CKD?
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Background: Because uremic symptoms and manifestations vary among patients with advanced chronic kidney disease, it is sometimes difficult to decide on the timing of dialysis initiation only from uremic symptoms. We attempted to investigate whether anion gap (AG) that may reflect the accumulation of total organic acids in uremia can be a marker of uremia and may predict the timing of dialysis initiation.

Methods: This study included pre-dialysis patients who attended to our hospital for more than six months prior to the beginning of hemodialysis (HD), and retrospectively analyzed the relationship between their serological data, AG, and various uremic symptoms. The AG was calculated as the corrected AG (cAG) = Na-Cl-HCO3

(results).

Results: A total of 283 patients [diabetes mellitus: 136 (48.1%), nephrosclerosis: 66 (23.3%), glomerulonephritis: 36 (12.7%)] were included in this study. The most common clinical symptom before dialysis initiation was fluid overload, which was seen in 134 patients (47.3%), followed by anorexia 104 patients (36.7%) and general malaise 96 patients (33.9%). The cAG began to increase 3 months before the initiation of HD (14.2 mmol/L), which showed a rapid increase just before the initiation, and was correlated with uremia and fatigue, better than fluid retention. Of note is that cAG was most significantly associated with dialysis initiation among various factors. The ROC of cAG for dialysis initiation showed the highest value of AUC 0.797 (95% CI 0.72 to 0.85, p=0.05), with a cutoff value of adjusted cAG 15.975 (sensitivity 0.689, specificity 0.786). Patients with advanced CKD?

Conclusion: Uremic symptoms and some serological markers including azotemia, metabolic acids, and hyperphosphatemia have been usually used to predict the magnitude of uremia and the timing of dialysis initiation. In our study, it is suggested that a rapid increase in cAG over 16 mEq/L may also be a good predictor of dialysis initiation within the subsequent 3 months.

PO1177

Mysterious Case of Recurrent Life-Threatening Lactic Acidosis
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Introduction: Patients living with diabetes are prone to type-II lactic acidosis, often presenting with profound acid-base derangements. The reason for lactate production is not obvious hence management can be challenging. We present a case of life-threatening recurrent lactic acidosis in a diabetic patient.

Case Description: A 67-year-old man with type 2 diabetes, hypertension, presented to the hospital with malaise for 2 days. He had been on metformin in the past but had recently switched to insulin. There was no history of alcohol ingestion nor use of herbal supplements. The lactic acid level was 34 mM/kg. Her arterial blood gas showed: pH < 7, HCO3 7.5 mmol/L, pCO2 16 mmHg. Phosphorus level was unusually high, 21.3 mg/dL, with unknown etiology. There was no history of enema or laxative use. A significant contributor of AG was lactate at 14.5, given her history of metformin use. Urine drug screen was positive for amphetamines. The volatile alcohol panel was positive for acetone; methanol, ethanol, ethylene glycol and isopropanol alcohol were not detected. Continuous venous hemofiltration (CVVH) was initiated. After 3 days, renal function started recovering, lactate and phosphorus levels normalized and AG closed. The patient did not need CVVH thereafter. Two months later, the patient was discharged to a nursing facility in a stable condition.

Discussion: Extremely elevated AG of 52 in this patient can be explained by a rise in concentrations of organic acid anions, lactate, ketoacids, hyperphosphatemia, and retention anions.
and his lactate level was 14.8 mmol/L. This was treated with supportive care alone. Six months later, he returned again with lactate of 13.5 mmol/L, worsening to 18.6 mmol/L. He improved after treatment with CRRT and supportive care. Alcohol levels, liver function tests, pyruvate, glutamate, metformin levels were all negative or normal. The thiamine level was not checked during his first admission. During the second visit, the value was normal but this was drawn after thiamine had been given. During the third visit, the thiamine level was noted to be less than 6 mmol/L. The patient was started on thiamine and has not had further episodes of lactic acidosis.

**Discussion:** Patients with diabetes are prone to excess lactic acid generation due to the decreased mitochondrial oxidative phosphorylation with relative hypoxia at the microvascular level. In addition, it has been noted that many diabetics are thiamine deficient. In the absence of thiamine, pyruvate cannot enter the Krebs cycle and is converted to lactic acid predisposing diabetics to type-B lactic acidosis. Thiamine is filtered in the glomerulus and is reabsorbed in the proximal tubule through the thiamine H+ antiporter. Long term use of diuretics has been associated with thiamine deficiency. However our patient was not taking any nor did he have chronic kidney disease or any evidence of malnutrition.

**PO1178**  
**Serum Bicarbonate and Gait Abnormalities in Older Adults**  
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**Background:** Low serum bicarbonate levels are associated with slow gait speed in older adults. However, the association between serum bicarbonate and other quantitative gait markers is unknown.

**Methods:** Quantitative gait assessments were performed on 330 community-dwelling, nondisabled adults aged 65 years old. Serum bicarbonate was categorized into tertiles (≥24, 25-27, ≥28 mEq/L). The relationship between bicarbonate and gait markers was investigated with multivariable linear regression adjusting for demographics, comorbidities including COPD, medication use, smoking status, BUN, and eGFR (CKD-EPI). Factor analysis on eight gait markers was performed to synthesize individual gait characteristics into unifying domains. CKD was defined as eGFR<60 mL/min/1.73 m2.

**Results:** There were 116 (35%), 146 (44%), and 68 (21%) participants in the low (mean bicarbonate 22 mEq/L), middle (26 mEq/L), and high (29 mEq/L) bicarbonate tertiles, respectively. After multivariable adjustment, compared with participants in the middle tertile, those in the low tertile had significantly slower speed (8.4 cm/s [95% CI 3.1-13.8]), shorter stride length (7.7 cm [95% CI 3.4-12.1]), and longer time in the double support phase of the gait cycle (0.03 s [95% CI 0.002-0.05]). Within the lowest tertile, there was a graded association of lower bicarbonate with greater severity of gait deficits (Figure 1). Associations were similar when limited to participants with CKD. Associations remained significant after additional adjustment for muscle strength, cognitive function, sensory nerve function, and balance. No significant associations were found for the high tertile or for other gait markers (e.g., cadence). Factor analysis produced 3 independent gait domains: pace, rhythm, and variability. Compared with the middle tertile, the low tertile had significantly poorer performance in the pace domain (0.3 standard deviation [95% CI 0.1-0.6]).

**Conclusions:** Low serum bicarbonate is associated with gait abnormalities in older adults.

**Funding:** Other NIH Support - NIA

**PO1179**  
**Bicarbonate Target in Treating Renal Acidosis: Is Higher Better?**  
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**Background:** Metabolic acidosis is commonly seen in patients with CKD from a decrease in ammonium excretion which gets buffered by the extracellular bicarbonate, hence, low plasma carbon dioxide is a surrogate of acidosis. treatment of acidosis (usually sodium bicarbonate to decrease the progression of, maintain bone health, nutrition status, In clinical practice, we aim for plasma bicarbonate of ≥2.2 mmol/L, the upper limit target is unclear.

**Methods:** This was a single-center retrospective chart review of CKD patients with acidosis from 2010-2017. Inclusion criteria were adult patients receiving NaHco3 for CKD-associated acidosis with baseline estimated glomerular filtration rate (eGFR) ≥25 and < 60 mL/min/1.73 m2 when starting NaHco3. Patients with glomerulonephritis, kidney transplant, acute kidney injury (not back to at least 75% of eGFR baseline) were excluded. Four groups were identified for comparison based on mean serum Co2 (in mmol/L), from outpatient measures during 3 years follow-up, group A (< 22), group B (22 - < 24), group C (24 - <25), and Group D (≥ 25). Albumin, urine protein-creatinine ratio (UPCR), PTH, and eGFR were compared, p-values were calculated by a one-way ANOVA model with Bonferroni correction.

**Results:** There were 383 patients with CKD-associated acidosis receiving NaHco3, 93 patients qualified for the study. Group A (n=21), group B (n=41), group C (n=13), and Group D (n=18). Racial demographics: 35=black (38%), 57=white (61%), 1=Other. Females 49 (53%). Median age 69 years. Follow-up 3 years. At baseline mean eGFR, UPCR, and albumin, and diuretics use and osteoporosis diagnosis in the four groups were similar (p = 0.46, 0.32, 0.15, 0.39, 0.36 respectively). Mean hemoglobin A1C in each group did not exceed 8.2. At 3 years of follow-up, changes in eGFR, UPCR, and osteoporosis status between the four groups were similar (p = 0.14, 0.27, 0.19 respectively). Change of albumin was significantly worse in group A comparing to groups B, C, and D (p = 0.007, 0.049 respectively), and average PTH was significantly worse in group A comparing to group C (p = 0.045).

**Conclusions:** In our cohort, all groups of treated CKD-associated acidosis (B, C, and D) showed no statistical difference in CKD progression, the severity of parathyroidism, developing osteoporosis, or nutrition status assessed after 3 years follow-up. Hence, higher Co2 targets don’t carry worse outcomes.

**PO1180**  
**Acute Metabolic Alkalosis due to Citrate-Containing Oral Rehydration Solution**  
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**Introduction:** Patients with ileostomies have high obligate gastrointestinal (GI) losses, predisposing to volume depletion and electrolyte derangements. Over-the-counter oral rehydration solutions (ORS) are advertised for dehydration. We present a case of acute metabolic alkalosis associated with an ORS containing citrate.

**Case Description:** 66 year old man with Crohn’s disease, status post small bowel excision, sigmoid colectomy with Hartman’s pouch, and ileostomy presented with weight loss of 35 pounds over 3 months. He was admitted for acute metabolic alkalosis associated with an ORS containing citrate.

**Conclusions:** In our cohort, all groups of treated CKD-associated acidosis (B, C, and D) showed no statistical difference in CKD progression, the severity of parathyroidism, developing osteoporosis, or nutrition status assessed after 3 years follow-up. Hence, higher Co2 targets don’t carry worse outcomes.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.
PO1181

Pseudo-Hypobicarbonatemia with Severe Hypertriglyceridemia Corrected by Insulin Infusion
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Introduction: Anion gap metabolic acidosis (AGMA) is a condition characterized by low serum bicarbonate and unaccounted anions in the blood. Lactate or ketones are the most common anions causing AGMA. Severe hypertriglyceridemia and paraproteinaemia can result in Pseudo-hypobicarbonatemia due to interference by these components when the commonly used enzymatic assay is utilized for serum bicarbonate measurement. The calculated bicarbonate derived from blood gas machines show accurate bicarbonate level. It is very important to recognize Pseudo-hypobicarbonatemia to avoid expensive work-up.

Case Description: A 42-year-old male patient with a past medical history significant for diabetes mellitus type 2, obesity, and hyperlipidemia. The patient presented with nausea, vomiting and epigastric pain. Physical examination was significant for tenderness in the epigastrium and xanthelasma. The basic metabolic profile (BMP) was significant for Na+ 127 mEq/L, Cl- 94 mEq/L, HCO3- 9mEq/L, glucose 408mg/dL, BUN 160mg/dL, creatinine 0.87mg/dL and AGAP 24. A lipid panel showed a cholesterol 461mg/dL, and triglycerides 4061mg/dL. Lipase and amylase were 1183U/L and 202U/L respectively. Urinalysis revealed trace ketones. CT abdomen revealed peripancreatic stranding. The patient was diagnosed with AGMA due to diabetic ketoacidosis and pancreatitis secondary to hypertriglyceridemia. An arterial blood gas analysis (ABG) subsequently revealed a pH 7.39, pCO2 40, PaO2 73 and a HCO3- 24. A significant dissociation between the calculated and measured bicarbonate was noted. Following aggressive lowering of the triglycerides, with Insulin infusion there was an immediate resolution of the pseudo-hypobicarbonatemia and anion gap metabolic acidosis.

Discussion: This measurement error is due to the mechanism by which the analyzer interprets the bicarbonate level in the serum. Most analyzers utilize either anion-selective electrode (ISE) or function via an enzymatic/photometric method. High amounts of lipid particles may cause light scattering altering the photometric analysis. This likely caused the discrepancy between the enzymatic/photometric measured serum bicarbonate and the calculated bicarbonate of the aqueous phase ISE analyzer used by the ABG. Clinicians should be able to recognize that its essential to obtain a blood gas sample for determination of the acid-base status to avoid expensive work up.

PO1182

Pseudohypobicarbonatemia in a Patient with Paraproteinaemia
Marvi M. Bukhari,1 Cary R. Boyd-Shiwari,2 Blaise W. Abramovitz.1 UPMC Mercy, Pittsburgh, PA; 1University of Pittsburgh Renal-Electrolyte Division, Pittsburgh, PA

Introduction: The first step in acid-base disorders’ diagnosis is obtaining measurement of blood bicarbonate (HCO3-), pH and partial pressure of carbon dioxide (pCO2) levels. Blood HCO3- levels are estimated via two methods: direct measurement of serum total carbon dioxide (TCO2), or via Henderson-Hasselbalch equation using arterial blood and directly measuring pH and pCO2 levels. With the enzymatic method, there have been reported cases of falsely low serum HCO3- due to interference by elevated triglyceride levels, but only two cases have been reported of spuriously low serum HCO3- due to interference by paraproteins.

Case Description: A 74-year-old male with a history of bladder carcinoma in situ and hypertension presented with complaints of malaise after a recent bladder irrigation. Basic metabolic panel (BMP) was unremarkable except for a HCO3- of 8 mmol/L measured using a Siemens Vista (SV) enzymatic chemistry analyzer. He was hospitalized for high anion gap metabolic acidosis with anion gap of 22. He was started on intravenous NaHCO3 (150 mEq/L) after nephrology was consulted. Repeat serum HCO3- was 11 mmol/L the next day with transition to oral NaHCO3 650 mg therapy thrice daily. On outpatient follow-up, he had low serum HCO3- ranging from 8-11 mmol/L (using SV analyzer) despite his reported compliance with NaHCO3. He was evaluated by another nephrologist with repeat BNP and an arterial blood gas (ABG). The results revealed a serum HCO3- of 8 mmol/L in contrast with ABG pH of 7.41 and HCO3- of 25 mmol/L. Due to the discrepancy, his serum HCO3- was analyzed at a different facility using a Beckman Coulter analyzer which revealed a normal serum HCO3- level of 21 mmol/L. He was hospitalized for near-total enterectomy and colectomy on total parenteral nutrition with a venting gastric tube. The patient was discharged home without diuretics and loop diuretics contributed to the development and maintenance of metabolic alkalosis. The loss of gastric acid in the G-J tube, but volume depletion, hypokalemia, AKI, high protein tube feeds, lack of respiratory compensation due to ventilator dependence and loop diuretics contributed to the development and maintenance of metabolic alkalosis.

Discussion: Paraproteins have been reported to cause interference with multiple laboratory test results. Paraproteins in our case may have resulted in artifactual error of serum HCO3- by direct interaction with assay reagents, binding of paraproteins to an assay reagent, or turbidity caused by the precipitation of the monoclonal proteins. Our case highlights the importance of being aware of this phenomenon of pseudohypobicarbonatemia that can occur with certain chemical analyzers.

PO1183

Proton Pump Inhibitor (PPI) for the Treatment of Metabolic Alkalosis due to Gastric Losses
Raphael J. Rosen, Heedekan Han, Sindhuri Prakash-Polet, Yonatan A. Peleg. Columbia University Irving Medical Center, New York, NY

Introduction: Gastric losses of hydrochloric acid can result in severe metabolic alkalosis (met alk). We describe two cases where patients with significant losses of gastric secretions presented with severe met alk and AKI. In both cases, PPI therapy was used to reduce the volume of the gastric secretions with excellent effect.

Case Description: Patient 1: A 44-year-old woman with Gardner Syndrome with near-total enterectomy and colectomy on total parenteral nutrition with a venting gastric tube (G-tube), presented with met alk (HCO3 30 meq/L and AKI (Scr 4 mg/dL). Met alk persisted despite normal saline (NS) administration and gastric tube losses ranged from 4-8 liters per day. Twice daily intravenous PPI was started with immediate decrease of gastric losses and normalization of HCO3. This patient was admitted one year later (off PPI therapy) with a similar derangements and resuming PPI therapy caused similar improvement. Patient 2: A 59 year-old man with gastric outlet obstruction and venting G-tube presented with met alk (HCO3 47 meq/L) and acute kidney injury (Scr 4.5 mg/dL from 1.3 mg/dL). Met alk persisted despite NS administration and his gastric tube losses ranged from 4-11 liters per day. Diurnal intravenous PPI was started with decrease of gastric losses and normalization of HCO3. This patient presented again to the hospital one month later with normal HCO3 on PPI therapy. Both patients’ bicarbonate and gastric fluid output trend relative to PPI therapy is detailed in figure 1.

Discussion: There are few reported cases of PPI therapy for metabolic alkalosis due to gastric losses. Generally, met alk that occurs due to gastric losses is readily rectified by increased renal bicarbonate excretion, but this compensatory mechanism is limited in the setting of AKI. We report two cases in which PPI therapy successfully decreased the quantity of gastric fluid losses and rapidly improved metabolic alkalosis.

Discussion: A 30-year-old male with Duchenne muscular dystrophy, chronic respiratory failure on mechanical ventilation via tracheostomy, gastrojejunoanostomy (G-J) tube dependent and genetic cardiomyopathy presented with drowsiness and lethargy for last 2 days per mother. His tube feed regimen was Nutren 1 can with 120 cc free water 4 times/day. He was recently started on Lasix 20 mg daily. Initial labs showed blood pH of 7.81, bicarb 66 and PCO2 53. He had AKI with Creatinine (Cr) of 2.66, BUN 266 and Crystatin C 11. His baseline Cr was 0.9-1.1. UA showed 3+ protein and no sediment. Urine (Ur) sodium 87, Ur chloride <15, Ur Cr <10 and Ur Ph was 9. Chest Xray showed cardiomegaly with mild venous congestion and kidney ultrasound showed bilateral small echogenic kidneys. He was treated with normal saline (NS) IV q8h 100 cc/hr, acetazolamide IV, potassium IV, proton pump inhibitor to decrease gastric acid and minute ventilation was increased to allow for compensatory hypercapnia. AKI improved with adequate diuresis and PH normalized (Image 1) by day 5. He had hypernatremia after 24 hours of IV NS and fluid were changed to hypotonic + free water via G-J tube. High daily output of ~700cc was recorded from the G-J tube. He was discharged home without diuretics and tube feeds were changed to Suplena + increase free water but was re admitted in 1 week with hypernatremia and severe metabolic alkalosis. He underwent G-J tube exchange during 2nd admission followed by persistent normalization of blood PH.

Discussion: This is a unique case of extreme metabolic alkalosis primarily due to the loss of gastric acid in the G-J tube, but volume depletion, hypokalemia, AKI, high protein tube feeds, lack of respiratory compensation due to ventilator dependence and loop diuretics contributed to the development and maintenance of metabolic alkalosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
We corrected his metabolic alkalosis and AKI with cautious use of IV fluids and furosemide. Chart review suggested that CSB implanted antibiotic spacers. CSBs are used for periprosthetic joint infections for new bone formation hydrophilic crystals used to deliver antibiotics locally, are one solution to prevent such complications. Hypercalcemia post-CSB placement is a rare complication that has only been presented in the literature a handful of times. We report on a such a patient, illustrating the importance of surgical history in investigating the cause of hypercalcemia.

Methods: From the MIMIC III v1.4 database, we paired chemistry panel iCa (mg/dL), Alb (g/dL), Na, and iCO2 values with panel iCa values (ref range: 1.12-1.32 mM) measured up to 20 min. apart. Limiting each pt. to the most closely-timed pair left 405 pairs (median:10 min apart). We calculated cCa (iCa +0.64×(4-Alb)) and ICaEST = 0.901×iCa -0.034×Alb -0.0042×Na -0.0073×Cl +0.0047×(iCO2) and compared their ROC curves (area(%)SE) for detecting iCa (CcA<1.10; rate=33.1%), and high iCa (1%Ca) (Ca<1.32; rate=3.8%).

Results: ICaEST was better than cCa by ROC analysis for both iCa (0.334±0.007 vs 0.752±0.008; p<10^-6) and 1%Ca (0.975±0.004 vs 0.963±0.006; p<0000). The table compares the sensitivity and specificity (SENS/SPEC) and positive and negative predictive values (PPV/NPV) of ICaEST and cCa at similar cutoffs. ICaEST overestimated iCa by 0.04 mM (1.17±0.002 vs 1.137±0.002; p<10^-6), a bias that was fairly consistent across the full prediction range.

Conclusions: The ICaEST model is superior to cCa in ranking critically ill pts for both iCa and 1%Ca. It can help clinicians decide when to directly measure iCa. ICaEST overestimated iCa but applying a local correction of -0.04 would make its absolute predictions accurate, and averaging, in the ICU setting.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Discussion: One of the rare and underappreciated causes of severe hypercalcemia is granulomatous hypercalcemia. Vigilant monitoring of calcium levels pre and post CSB placement is indicated, particularly in patients with a history of CKD. It has been hypothesized that there is a dose-dependent relationship between CSB volume and hypercalcemia, and limiting CSB to less than 40ml per operation may be beneficial. A 10ml pack of CSB contains 5.73 grams of elemental calcium which is released over a 30-60-day interval. There is limited information on the mechanism of hypercalcemia in CSB use, so further studies need to be implemented. It is crucial for physicians to have a high suspicion for CSB induced hypercalcemia post-arthroplasty as CSB use expands.

PO1189
Hypercalcemia in a Patient with Visceral Leishmaniasis (VL) and Immune Reconstitution Inflammatory Syndrome (IRIS)
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Introduction: Hypercalcemia is a relatively common clinical problem with a wide range of etiologies. We report an unusual case of hypercalcemia due to visceral leishmaniasis triggering immune reconstitution inflammatory syndrome in a patient with AIDS.

Case Description: A 45-year-old male with history of previously treated VL complicated by a relapse now on suppressive amphotericin presented with 2 weeks of poor appetite, weight loss, and malaise. Recent history was notable for AIDS restarted on Triumeq in the preceding 2 months with slow recovery of CD4 count to 18 but robust reduction in HIV viral load. He denied other infectious symptoms. Labs were notable for AKI, calcium of 13.1, and pancytopenia. Work up revealed low PTH, low calcidiol, elevated serum CRP levels and high-normal serum creatinine levels with bone marrow biopsy revealing non-necrotizing granulomas. Remainder of infectious work up including mycobacterium, histoplasma, and fungal cultures all remained negative. Of note, CD4 count rebounded to 354 during his month-long stay. He was ultimately diagnosed with IRIS secondary to VL leading to granulomatous hypercalcemia. Initial therapy consisted of fluids which resolved AKI and improved calcium. However, he proved to be fluid dependent as attempts at weaning would result in rise in calcium and creatinine. Definitive therapy consisted of steroids which resolved his hypercalcemia allowing him to come off fluids. Apoptosis improved and fatigue resolved over course of his stay with stabilization of calcium levels and creatinine returning to baseline. He was continued on suppressive Amphotericin B for VL.

Discussion: Granuloma formation is a known effect of leishmania infection to combat the invading parasites. Presumably, such inflammation could lead to hypercalcemia via increased conversion of calcidiol to calcitriol. To our knowledge, this is the first case of hypercalcemia caused by VL in humans. It was likely triggered by the reconstitution of his immune system given recent re-initiation of anti-retroviral therapy and rebound of CD4 cell count. Initial management consisted of fluids and bisphosphonates with definitive management consisting of steroids and amphotericin. We report this novel case of hypercalcemia in hopes of expanding the literature on the various potential manifestations of VL, particularly in the setting of IRIS and AIDS.

PO1190
Systemic Sarcoidosis Presenting with Hypercalcemia
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Introduction: Sarcoidosis is an idiopathic autoimmune illness that typically presents with pulmonary involvement but can affect virtually any organ. This often makes it challenging to diagnose as its manifestations can be quite varied. We report an interesting case of systemic sarcoidosis presenting with hypercalcemia of unclear mechanism.

Case Description: A 53-year-old Caucasian male presented to the clinic with polyuria, forgetfulness and weight loss. Medical history included hypercalcemia with recurrent nephrolithiasis, diabetes and positive ANA (titer 1:160) without any prior history of constitutional, respiratory or joint symptoms. Serum calcium returned 13 mg/dl. The patient also had an AKI and an elevated ALP. Further workup revealed a suppressed PTH, normal 25-OH and 1,25-OH vitamin D, but a borderline elevated PTHrp (2.5 pmol/L [0.2-3.0 pmol/L]). This prompted a CT CAP with contrast to rule out malignancy that instead showed mediatinal lymphadenopathy, heterogeneous liver enhancement suggestive of cirrhosis and an enlarged, nodular spleen. Transbronchial lymph node biopsies were normal and an extensive infectious and malignancy workup remained negative. The patient was given fluids followed by zoleodronate with resolution of hypercalcemia and AKI. A liver biopsy was ultimately pursued which showed non-caseating granulomas. The patient was prescribed steroids with improvement in symptoms and normalization of ALP.

Discussion: In patients with sarcoidosis, the development of hypercalcemia is thought to be mediated via aberrant activation of vitamin D leading to calcitriol excess. Our patient’s calcitriol level was normal and hypercalcemia may also occur in the absence of elevated levels. Possible described mechanisms include “inadequate normal” calcitriol concentration without elevation in systemic levels, elevated PTHrp and direct action of pro-inflammatory cytokines causing osteolysis.

CT with contrast showing heterogenous liver enhancement and a nodular spleen.

PO1191
Disseminated Histoplasmosis Presenting as Severe Hypercalcemia
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Introduction: Hypercalcemia (HC) is a significant complication of Disseminated Histoplasmosis (DH). While there are case reports on DH causing HC in immunosuppressed patients including HIV and chemotherapy, there are very rare case reports on DH causing HC in Non-immunosuppressed hosts. The diagnosis of DH in HC may be delayed due to other differential diagnoses such a Sarcoisosis leading to prolonged and worsening hypercalcemia and subsequent renal failure. We report a case of HC in a patient who presented with generalized skin ulcers and bilateral adrenal masses. The initial manifestation of DH with HC, painful skin ulcers, bilateral large lobulated adrenal masses, prompted an initial concern for sarcoidosis. After presenting to our institution 5 months later, a diagnosis of DH was made as the cause of his Hypercalcemia.

Case Description: A 58-year-old male with new onset generalized skin rash was diagnosed with HC, empirically treated with prednisone for sarcoidosis due to elevated 1.25 di hydroxy Vitamin D, 5 months ago at an outside hospital. After starting prednisone, his skin lesions progressed to disseminated painful ulcers and was referred to our institution after developing AKI with a serum creatinine of 4.6mg/dl (Cr 1.6mg/dl, 5 months ago) calcium 14mg/dl, PTH 2pm/mL. CT abdomen revealed large lobulated bilateral adrenal masses. Bone marrow biopsy revealed non-necrotizing granulomas with yeast form fungal organisms on GMS stain. A Shave skin biopsy of an abdominal ulcer revealed fungal yeast forms consistent with histoplasmosis, associated with ulcers on GMS stain. Urine Histoplasma antigen positive. Adrenal mass biopsy revealed necrotic material and fibroconnective tissue. DH was initially treated with IV liposomal amphotericin and transitioned to oral Itraconazole. At the time of discharge, calcium was 9.8 mg/dl and serum creatinine was 2.9mg/dl.

Discussion: Hypercalcemia, in the setting of elevated 1.25 di hydroxy Vitamin D levels, prompts concern for granulomatous disease. Sarcoidosis is a common etiology, however, other causes must be entertained. The cluster of findings of adren al non-casing granulomas coupled with diffuse skin ulcers with hypercalcemia should prompt the provider to consider infectious etiologies such as disseminated histoplasmosis as early diagnosis and prompt treatment can result in improved outcomes.

PO1192
Electrolyte Disturbances Among Those with Malignancy on Anti-Neoplastic Agents
Mihoko Murashima, Atsuki Ide, Minamo Ono, Masashi Mizuno, Taiezu Suzuki, Takayuki Hamano. Nagoya Shiritsu Daigaku, Nagoya, Japan.

Background: The clinical characteristics of electrolyte disturbances among patients with malignancy in contemporary cohorts are lacking.

Methods: This is a retrospective cohort study on 2644 patients with malignancy on anti-neoplastic agents from 2019 to 2020. Anti-neoplastic agents associated with electrolyte disturbances were examined by multi-level mixed-effects logistic regression analyses. The data were adjusted for age, sex, serum albumin, eGFR, kinds of malignancy, and other medications which potentially affect electrolytes.

Results: Mean age was 64.8 (15.8) years, 55.5% were male, and median eGFR was 72.9 (58.1-88.1) mL/min/1.73m². The prevalences of hyponatremia (Na ≤130 mEq/L), hypomagnesemia (Mg ≤1.5 mg/dl), hypophosphatemia (P ≤2.0 mg/dl), and hypokalemia (K ≤3.0 mEq/L) were 2.1 (1.8-2.2), 2.0 (1.7-2.3), 1.7 (1.6-1.9), and 1.2 (1.1-1.4) events/100 patient-measurements, respectively. The use of bortezomib was associated with hypomagnesemia (OR: 3.04 [1.96-4.71]) and three immune checkpoint inhibitors were significantly associated with hyponatremia. The use of cetuximab and gemcitabine were strongly associated with hypomagnesemia (OR 11.79 [7.56-18.38] and 5.95 [3.36-10.55].

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
respectively). Other agents associated with electrolyte disturbances were shown in Table. Other than anti-neoplastic agents, lower albumin levels were consistently associated with development of electrolyte disturbances.

**Conclusions:** Electrolyte disturbances were common and associated with the use of novel anti-neoplastic agents among those with malignancy. Identifying the agents and patient population at high risk of developing electrolyte disturbances is important in taking appropriate preventive measures and monitoring for those undergoing treatments with anti-neoplastic agents.

**PO1193**

**Resistant Hyrophosphatemia with Vitamin D Deficiency**

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**Introduction:** The renal regulation of phosphate homeostasis is mediated mainly by reabsorption of P by NaPi-IIc in the proximal tubule, whereas intestinal absorption is mediated by NaPi-IIb. Normally, about 2/3 of dietary intake (1500 mg/day) is absorbed, but when given by mouth as Na or K phosphate, absorption is nearly 100% in a normal person. We report here a patient with severe hyrophosphatemia due to phosphate malabsorption caused by prior gastric bypass surgery along with vitamin D deficiency.

**Case Description:** A 34 year old African American female with past medical history of benign carcinoma of thyroid, pernicious anemia, Hashimoto thyroiditis, and gastric sleeve surgery for morbid obesity 3.5 years ago, was admitted for acute dizziness and lightheadedness at rest without vertigo. Initial labs were: BUN 4 mg/dL; creatinine 0.6 mg/dL; Ca 9.2 mg/dL; Mg 2.17 mg/dL; P 1.3 mg/dL; 25-OH vitamin D 10.88 ng/mL; 1,25(OH)2 vitamin D 15.35 pg/mL; PTH 7.77 pg/mL; urine P 77 mg/dL; urine creatinine 342.51 mg/dL. She was being given vitamin B12 injections for her pernicious anemia. She was treated with oral Na and K phosphate solution containing 560 mg of P, 320 mg of Na, and 500 mg of K in each dose for every 4 hours, and once daily dose of IV K phosphate containing 465 mg of phosphate for 14 days. She was also treated with 800 units daily of Vitamin D2 daily. Serum phosphate remained persistently low around 1.8 mg/dL despite the above treatment.

**Discussion:** Hyrophosphatemia in our patient was caused by impaired intestinal absorption of phosphate, and inappropriately increased urinary excretion due to secondary hyperparathyroidism due to vitamin D deficiency. The total daily amount of phosphate the patient received while in the hospital was 3825 mg per day. A 24 hour urine excretion of P estimated from urine creatinine concentration (342 mg/dL), assuming normal GFR (180 L/day), is very low (245 mg/day). Although P administered as Na or K salt is well absorbed in a normal person, she was unable to absorb P likely due to the gastric sleeve surgery causing rapid emptying of the gastric content, simulating the dumping syndrome, resulting in diarrhea by unabsorbed Na and K phosphate. Further impairment in intestinal P absorption may have been caused by vitamin D deficiency due to the inadequate dosing (800 units daily) and the inappropriate vitamin D type (Vitamin D2 instead of D3).

**PO1194**

**Severe Hyrophosphatemia Induced by Oncogenic Osteomalacia**

Abdullah Jalal, Ryan P. Brown. Overlook Medical Center, Summit, NJ.

**Introduction:** Oncogenic Osteomalacia (Oncom) is an uncommon paraneoplastic syndrome characterized by FGF-23 overexpression from benign mesenchymal tumors causing severe hyrophosphatemia. Very few cases of Oncom with concomitant paraneoplastic syndromes have been described. Herein we present a rare case of carboanin-associated hyponatremia in the setting of ScaADH-induced chronic hyponatremia unmasking an even rarer secondary paraneoplastic syndrome; oncogenic osteomalacia.

**Case Description:** A 52 year old male with past medical history of chronic hyponatremia on salt tablets secondary to recently diagnosed metastatic small cell lung cancer was admitted for initiation of chemotherapy with carboplatin/etopside. Two days after completing cycle 1 the patient developed acute hyponatremia; serum Na decreased from 141 to 129 mEq/L. Serum electrolytes were (mEq/L): K 3.9, Cl 94, HCO3 28, BUN 30, Cr 6.47. Cortisol (17.8 ug/dL) and TSH (2.28 uIU/mL) were within normal limits. Urine studies noted (mEq/L): Na 75, Cl 69, K 43.5, elevated osmolality 860 mOsm/kg. Endoscopy of acute hyponatremia was attributed to platinum chemotherapy in the setting of SCC-associated ScaADH and patient was treated with tolvaptan after several days of non-response to fluid restriction and urea. Patient’s hyponatremia subsequently corrected but was incidentally noted to have severe hyrophosphatemia (<1 mEq/L) refractory to aggressive IV and PO phosphate repletion. ALP was elevated 279 U/L, corrected Ca 10 mEq/L, low 25(OH) vitamin D 23.8 ng/mL, normal PTH 45.6 pg/mL and PTHrP <0.4 pmol/L. Urinary fractional excretion of phosphorus was increased at 24%. An FGF-23 level obtained 12 days after completing cycle 1 of carboplatin- etopside was considerably elevated at 219 pg/mL. Thus, the patient was diagnosed with oncogenic osteomalacia.

**Discussion:** This case highlights a unique and diagnostically challenging patient presentation of severe hyrophosphatemia in the setting of dual paraneoplastic syndromes. Oncom should be considered in the differential for severe refractory hyrophosphatemia. This occurs via FGF-23 mediated downregulation of PCT Na-Pi transporters and 1a-hydroxylase causing renal phosphate wasting and reduced 1,25-dihydroxyvitamin D levels. Over time chronic hyrophosphatemia impairs bone mineralization causing osteomalacia. Measurement of the fractional excretion of phosphorus is critical and FGF-23 levels should be obtained to confirm diagnosis.

**PO1195**

**Phenotypes of Patients with Abnormal Phosphate on Admission by Consensus Clustering and Associated Mortality Risks**

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**Background:** Hospitalized patients with abnormal phosphate are heterogeneous and cluster approaches may identify specific homogeneous groups. This study aimed to cluster patients with abnormal phosphate on admission using unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

**Methods:** Consensus cluster analysis was performed on hospitalized adult patients with abnormal phosphate on admission, based on clinical and laboratory data. We determined each cluster’s key features using the standardized mean difference. We assessed the association of the clusters with hospital and one-year mortality.

**Results:** Cluster 2 patients with hyrophosphatemia had older age, higher comorbidity burden, hypertension, diabetes, coronary artery disease, lower eGFR, and more acute kidney injury (AKI) (Fig 1a). Cluster 2 patients with hyperphosphatemia had older age, more admission for kidney disease, hypertension, end-stage kidney disease, AKI, and higher admission K+, Mg2+, or PO2 levels (Fig 1b). Both cohorts in cluster 2 had higher one-year mortality while hyperphosphatemic cluster 2 patients had higher hospital mortality (Fig 2).

**Conclusions:** The cluster analysis identified clinically distinct phenotypes with differing mortality risk in hospitalized patients with abnormal phosphate on admission. The age, comorbidities, and kidney function were key features.
POI196

Anatto Leaf Tea Intoxication: An Unusual Cause of Green Urine
Eduardo Valle, Rayra G. Ribeiro, João Lucas M. Gorzoni, Guilherme P. Santa Catharina, Bernardo V. Reichert, Marcia Fernanda Arantes de Oliveira, Victor F. Seabra, Paulo R. Lins, Igor Smolentzov, Camila E. Rodrigues, Lucia Andrade. Hospital das Clínicas, University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Introduction: The roots and leaves of the annatto (“urucu”) tree (Bixa Orellana) are used by the lay population in the treatment of many diseases. We describe a case of AKI with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use.

Case Description: A 59-year-old male without known comorbidities presented with a 2-week history of severe diarrhea. Three days prior to admission, he was diagnosed with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and urine cultures were negative and there was no history of drug use. He was discharged on day 14 with no remaining F+E imbalance or renal dysfunction.

Discussion: The diuretic effect of annatto leaf extracts has been shown in experimental models. To our knowledge, this is the first report of severe AKI and F+E imbalance due to annatto leaf tea use. In our patient, AKI was caused by the annatto leaf tea use. Patients frequently describe mass symptoms & reduced quality of life (QoL) that correlate with large (≥5cm diameter) organ cysts in ADPKD/ADPLD. Since 1/18/2017, we have studied the safety & impact of cyst drainage followed by sotradecol foam sclerotherapy (SFS) to treat symptomatic, large cysts.

Results: We performed 148 SFS procedures among 68 cases (mean age 55yr 77% Female, mean 2.2 procedures per pt): 53 (77.9%) with ADPKD/ADPLD, 5 (7.4%) with ADPLD, & 10 (14.7%) with cystic disease NOS. PLD-Q scores improved by 7.7 (IQR 0.1, 24.8) (p=0.012) at mo 12. A subgroup (13 patients) (mean age 54.7yr, 69% F) have undergone multiple sequential SFS procedures: 10 (77%) with ADPKD/ADPLD, 2 (15%) ADPLD, & 1 (8%) cystic disease NOS. Among 5 with multiple kidney procedures, median kidney volume decreased by 135mL/yr. Among 5 with multiple liver procedures, median liver volume decreased by 114mL/yr. SFS was well tolerated with low complication rates.

Conclusions: SFS directed at large, symptomatic liver and kidney cysts was well tolerated, improved QoL at 12 months, & decreased early satiety, SOB, pain & fullness. Furthermore, multiple sequential SFS procedures are feasible, efficacious, and have an acceptable safety profile.

Funding: NIDDK Support, Private Foundation Support

Table 1.

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<th>Parameter</th>
<th>Admission</th>
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<td>14.4</td>
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<td>Calcium (mg/dL)</td>
<td>11.5</td>
<td>11.4</td>
<td>10.6 - 11.8 mg/dL</td>
</tr>
</tbody>
</table>

Fig 1. The Manhattan plot of standardized differences in the hypophosphatemia (a) and hyperphosphatemia cohort (b).

Fig 2. The hospital mortality (a) and one-year mortality (b) in the hypophosphatemia cohort. The hospital mortality (c) and one-year mortality (d) in the hyperphosphatemia cohort.

POI197

Foam Sclerotherapy for Directed Treatment of Symptomatic Cysts in Autosomal Dominant Polycystic Kidney and Liver Disease
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Background: Patients frequently describe mass symptoms & reduced quality of life (QoL) that correlate with large (≥5cm diameter) organ cysts in ADPKD/ADPLD. Since 1/18/2017, we have studied the safety & impact of cyst drainage followed by sotradecol foam sclerotherapy (SFS) to treat symptomatic, large cysts.

Methods: In this single-center, single-arm, prospective observational study, ADPKD and ADPLD patients with compressive symptoms due to liver or kidney cysts are referred for SFS. Small volumes (20cc max) of 3% sotradecol sclerosant admixed with air are injected (fluoroscopy-guided under local anesthesia) to ablate the epithelial cyst lining. QoL measures using polycystic liver disease Qol tool (PLD-Q) & organ volumes (planimetry using CT/MR) are recorded at baseline & 12+ months post-SFS. Changes over time were tested using Wilcoxon tests and confirmed using repeated measures mixed models. Improvements >0.5 SD were considered clinically meaningful.

Results: We performed 148 SFS procedures among 68 cases (mean age 55yr 77% Female, mean 2.2 procedures per pt): 53 (77.9%) with ADPKD/ADPLD, 5 (7.4%) with ADPLD, & 10 (14.7%) with cystic disease NOS. PLD-Q scores improved by 7.7 (IQR 0.1, 24.8) (p=0.012) at mo 12. A subgroup (13 patients) (mean age 54.7yr, 69% F) have undergone multiple sequential SFS procedures: 10 (77%) with ADPKD/ADPLD, 2 (15%) ADPLD, & 1 (8%) cystic disease NOS. Among 5 with multiple kidney procedures, median kidney volume decreased by 135mL/yr. Among 5 with multiple liver procedures, median liver volume decreased by 114mL/yr. SFS was well tolerated with low complication rates.

Conclusions: SFS directed at large, symptomatic liver and kidney cysts was well tolerated, improved QoL at 12 months, & decreased early satiety, SOB, pain & fullness. Furthermore, multiple sequential SFS procedures are feasible, efficacious, and have an acceptable safety profile.

Funding: NIDDK Support, Private Foundation Support
Development of AL01211, a Novel Glucosylceramide Synthase Inhibitor, to Treat Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: AL01211 is a novel glucosylceramide synthase inhibitor (GCSi) that is undergoing clinical development as a potential disease modifying agent for ADPKD. The primary objective of this study was to determine the safety, pharmacokinetics (PK), and efficacy of AL01211 in healthy volunteers.

Methods: A 7-day, ascending dose study in healthy volunteers to evaluate AL01211 PK and safety. PK studies were conducted once daily, oral administration. AL01211 has low renal clearance in rats. AL01211 dose proportionally distributes to peripheral tissues and is not excreted in the urine. AL01211 is more potent with single digit nanomolar potency, has greater reduction of GSL (∼85%), is not subject to kidney clearance and does not enter the brain. Phase I clinical trials, consisting of Phase IA (single ascending dose study in healthy volunteers), Phase IB (14-day multiple ascending dose study in healthy volunteers), and Phase IC (28-day biomarker study in ADPKD patients) are underway.

Funding: Commercial Support - AceLink Therapeutics

The Tyrosine Kinase Inhibitor Nintedanib Ameliorates Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and is characterized by progressive growth of fluid-filled cysts in the kidneys. ADPKD is generally diagnosed by imaging studies and may be delayed to P5 affecting mainly collecting tubules, causing death at P15, generating life expectancy. Mice Pkd1 f/f Pkhd1 Cre mice and in for 8 weeks starting at the age of 3 months in Pkd1 f/f mice. In vitro studies were performed using primary culture human ADPKD renal cystic epithelial cells and renal myofibroblasts.

Results: Nintedanib treatment significantly reduced kidney-to-body weight ratio, cyst renal index, cystic epithelial cell proliferation and blood urea nitrogen levels compared to vehicle treated Pkd1 f/f Pkhd1 Cre mice. Western blot data indicates reduction in the phosphorylation of ERK1/2, AKT, STAT3 and mTOR activation and pro-fibrotic factors, including Yes-associated protein (YAP), c-Myc and Cyclin D1 protein levels. Moreover, nintedanib treatment significantly reduced renal fibrosis in Pkd1 f/f mice, however, fibrosis in Pkd1 f/f Pkhd1 Cre mice remained unaffected. In vitro data suggests that nintedanib significantly reduced proliferation and cyst size of human ADPKD cystic epithelial cells as well as cell viability and migration of human ADPKD renal myofibroblasts.

Conclusions: The results suggest that Nintedanib is effective in reducing cyst growth and may be repurposed to treat ADPKD.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
collecting tubular origin and survived until P12-15. While SBR reached Pkd1 therapeutic levels in the mild SBR/Pkd1-/-, the additional Tg copies suggest the presence of regulatory region within Pkd1 gene-body. Renal cysts in SBR/Pkd1-/- and SBR/Pkd1-/- co-detected by RNAscope and IF, arise likely from insufficient and chimeric Pkd1 re-expression. These analyses also shed light on Pkd1 spatio-temporal expression pattern with highest expression in collecting tubules during renal maturation that shifts to distal tubules following maturation.

Conclusions: Pkd1 is regulated by elements both upstream for spatio-temporal pattern and intragenic sequences for expression levels. The renal-specific SB minimal regulatory region is sufficient for therapeutic correction in one copy Tg. Our study demonstrates that Pcd re-expression can substantially delay cystogenesis and markedly extend lifespan.

Funding: Government Support - Non-U.S.

PO1202
Wheat-Gluten Diet Attenuates Ccl2-Mediated Immune Response and Slows Polycystic Kidney Disease
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Background: Disease severity of autosomal-dominant polycystic kidney disease (ADPKD) is highly variable, even among families with the same gene mutation. A high protein diet is a well-recognized ADPKD progression-accelerating factor. Dietary protein composition is important, as pre-clinical studies have shown a soy protein-based diet slows kidney cyst formation in rodent PKD models. Recruitment of macrophages in the kidney is known to promote cystogenesis in PKD. We hypothesize that type of protein in the diet may serve as a potential environmental stimulant to immune response and cyst growth.

Methods: Using tamoxifen-inducible Pkd1-global knockout mice, we fed the mice with either a high casein-protein (animal-based protein: 60%), a low casein-protein (6%) or a high wheat-gluten (plant-based protein: 60%) for a total of 1 week or 6 weeks. Some mice fed a high casein protein diet were treated with liposomal clodronate or saline for a total of 5 weeks. Mice were euthanized and kidney cyst area, number of macrophages and chemokine/cytokine levels were measured.

Results: Pkd1-knockout mice fed a high casein diet increased the number of kidney macrophages, expression of macrophage-recruiting chemokine Ccl2 (but not chemokines Csf1 or Ccl5), pro-inflammatory cytokine (Il6, Tnf-a) and accelerated cyst growth compared to counterparts fed an iso-caloric high wheat-gluten (WG) diet or a low casein diet diet. We found that in very early stages during dietary casein load (1 week after diet modification), cyst expansion precedes macrophage recruitment in the kidney, indicating that diet per se triggers early cyst growth rather than as a consequence of macrophage recruitment and inflammation. High protein diet fed Pkd1-knockout mice treated with liposomal clodronate, resulted in decreased number of macrophages, cytokine and fewer cysts.

Conclusions: Wheat-gluten diet fed Pkd1-knockout mice resulted in decreased the number of macrophages, suppressed levels of kidney Ccl2, but not Csf1 or Ccl5, and slowed cyst growth compared to counterparts fed an iso-caloric casein based diet. Dietary protein modification may suppress immune response and cyst growth in PKD.

Funding: NIDDK Support

PO1203
High Prevalence of Kidney Cysts in Hereditary Hypophosphatemic Rickets with Hypercalcemia
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Background: Hereditary Hypophosphatemic Rickets with Hypercalcemia (IHRH) is a rare monogenic disorder caused by SLC34A3 pathogenic variants, characterized by renal phosphate wasting, hypophosphatemia, hypercalcuria (HC), elevated 1,25-dihydroxyvitamin D, nephrocalcinosis (NC), and urinary stone disease (USD). Previously we reported a high prevalence of kidney cysts in CYP24A1 deficiency. Thus, in the current study, we characterized cyst prevalence in HHRH, another monogenic cause of HC, NC, and USD.

Methods: Medical records from Mayo Clinic and Rare Kidney Stone Consortium research results were queried for all patients with genetically confirmed HHRH diagnosis. Clinical characteristics and imaging data are summarized in table 1. Results: Among 12 patients with SLC34A3 pathogenic variants (7 monoallelic, 5 biallelic), 42% (5/12) were males. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). None had a family history of cystic kidney disease. Kidney cysts (Figure 1) were present in 75% (9/12), among whom median age at first kidney imaging and first cyst detection was 41 yrs (range 9-64).

Conclusion: We found a strong association between IHRH and kidney cysts. Similarities in the biochemical profiles of IHRH and CYP24A1 deficiency suggest elevated active vitamin D, and/or HC may be potential factors in cyst formation. Further studies are needed to evaluate the role of the SLC34A3 gene in cyst formation.

Funding: NIDDK Support, Private Foundation Support

PO1204
Dysregulated Tryptophan Metabolism Promotes Polycystic Kidney Disease Progression
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Background: Metabolic reprogramming is a feature and modifier of autosomal dominant polycystic kidney disease (ADPKD) progression. Moreover, immune cells regulate cyst growth. In cancer, a disease with parallels to PKD, the metabolic landscape created by tumors significantly impacts immune cell function and tumor growth. Yet, this link is unexplored in PKD. Here, we study tryptophan metabolism, a known immunosuppressive pathway, in cyst growth.

Methods: Metabolites were profiled in ADPKD patient plasma and kidneys of an orthologous ADPKD model (C57Bl/6J Pkd1^/-/-). We also crossed the ADPKD model to Ido1^/- mice, the enzyme metabolizing tryptophan to kynurenines, and inhibited Ido1 using the tryptophan analog 1-MT (400mg/kg, twice daily, orally). From these mice, kidney immune cells were profiled via flow cytometry.

Results: Tryptophan metabolites were significantly increased in Pkd1^/-/- mice at 3-, 6-, and 8-months compared to wild type and correlated with disease progression. Plasma levels of kynurenines significantly associated with HHTKV at baseline, and positively correlated with annual percent change of HHTKV in adult ADPKD patients. Ido1 levels were significantly increased in kidneys of PKD mice and patient cell lines. At 6-months of age, Pkd1^/-/Ido1^/- mice had significantly milder PKD compared to Pkd1^/-/Ido1^/- mice as measured by % KW/BW and cystic/iblritic index. Similarly, treatment of 1-month-old Pkd1^/-/Ido1^/- mice with 1-MT for 3 weeks slowed cyst growth; overall providing functional evidence of the pathway’s relevance to PKD. Kidney immune profiling of Pkd1^/-/-, Ido1^/- and 1-MT-treated mice revealed a significant reduction of resident macrophages, regulatory T cells, and immune checkpoint protein expression (PD-1/PD-L1), while the percentage of CD8^- T cells total T cells increased.

Conclusion: Our data highlight tryptophan metabolism as a novel dysregulated pathway in human and ADPKD and suggest that tryptophan metabolism are biomarkers of disease progression. Further, inhibition of the pathway presents a new treatment approach. Ido1 inhibitors are FDA approved for various cancers. Our data suggest a link between metabolic reprogramming, immune cell function, and disease progression, as Ido1 loss/inhibition impacted immune cell populations/pathways shown to regulate cyst growth.

Funding: NIDDK Support, Private Foundation Support

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392
PO1205

Creatine Kinase Elevation in Patients with Autosomal Dominant Polycystic Kidney Disease on Tolvaptan Treatment
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease worldwide. Studies such as the TEMPO 3:4 and 4:4 have demonstrated tolvaptan's (vasopressin V2 receptor antagonist) effectiveness in slowing the progression of this disease. The best described adverse effect seen with this treatment is drug-induced liver injury, however, creatinine kinase (CK) elevation has also been described anecdotally in a couple of case reports.

Methods: This is a prospective observational study of adult patients with rapidly progressive ADPKD on tolvaptan treatment under follow-up at Hospital Clinic de Barcelona from October 2018 to March 2021. Quantitative variables are described as mean and standard deviation, while qualitative ones are reported as absolute and relative frequencies.

Results: A total of 37 patients started treatment with tolvaptan during this period. In 34 of them, serum CK levels were measured as part of the monthly biochemical follow-up. A total of 29.11% (10 of 34) of the patients elevated this parameter with a mean of 1368.2 ± 2807.28 U/L. Seven patients had a transient elevation with a mean of 446.43 ± 359.22 U/L, which reversed upon dose decrease or treatment pause. However, treatment had to be interrupted in the remaining three patients (mean 3519 ± 5016.36). In one of them due to concomitant drug-induced liver injury and in the other two due to persistent CK elevation despite dose reduction or temporary treatment interruption. CK elevation was rarely related to exercise, although one patient reported a weekly intense cycling exercise with increased myalgia afterward) and was not significantly correlated with LDL levels, liver enzymes, calcium, potassium, urinary or plasma osmolarity.

Conclusions: By performing a general screening, we found that CK elevation is more frequently described previously in the literature, reaching significantly increased levels or producing symptomatology requiring definitive treatment interruption. Based on these results, although the studied sample is small, we suggest adding this parameter as a part of tolvaptan treatment’s follow-up, at the beginning of treatment and when increasing its dose, to promptly detect undesirable adverse effects and gain a better understanding of this phenomenon.

PO1207

Protein 4.1O Links Polycystin 1 to the Actin Cytoskeleton and Modulates Hippo Signaling
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Background: The majority of ADPKD patients have a PKD1 gene mutation. PKD1 codes for Polycystin-1 (PC-1). Cyst formation is caused by altered renal tubular cell proliferation. Protein 4.1 family members are actin adaptors, which link plasma membrane receptors to the actin cytoskeleton. Protein 4.1O (FRMD3) is a candidate gene for diabetic nephropathy. Furthermore, protein 4.1O has properties of a tumor suppressor. This study investigates the molecular and cellular properties of protein 4.1O as a potential ADPKD modifier and therapeutic target.

Methods: PC-1 full-length and truncation mutants were transiently expressed. PC-1 interaction with protein 4.1O and its truncation mutants were investigated. Truncation mutants cover the N- and C-terminal domains of protein 4.1O (Band 4.1, FERM, actin-binding domain and coiled coil domain). Communoprecipitations of protein 4.1O with PC-1 in IMCD cells were performed. Full-length protein 4.1O and F-actin were performed. The modulation of the PC-1 signaling properties by protein 4.1O were investigated in luciferase assays for c-myc and TEAD. FRMD3 core promoter regions were cloned into luciferase reporter. Results: Communoprecipitations show an interaction of protein 4.1O to PC-1 full-length. The C-terminus of PC-1 interacts with four isoforms of protein 4.1O (201, 202, 204, 207). The truncation mapping and isoform alignment identifies a potential leucine zipper domain in protein 4.1O as the C-terminal binding domain to PC-1. The N-terminal domain of protein 4.1O is also sufficient to mediate PC-1 interaction. Protein 4.1O C-terminus binds to F-actin and links the PC-1 C-terminus to the cytoskeleton. Protein 4.1O silences the PC-1 mediated transactivation of c-myc and hippo signaling (TEAD). Furthermore, F-actin desassociation influences the PC-1 induced hippo signaling. PC-1 activates the protein 4.1O prodeath activity.

Conclusions: Both, the FERM domain and leucine zipper containing coiled coil domain of protein 4.1O interact with the PC-1 C-terminus. The interaction of protein 4.1O links PC-1 to the actin cytoskeleton. The protein 4.1O interaction inhibits the PC-1 mediated propagation of c-myc and hippo signaling. Furthermore, protein 4.1O provides a F-actin based sensitivity to the PC-1 mediated hippo signaling. In summary, protein 4.1O shows features of an anti-cystogenic protein.

PO1208

Polycystin 2 Mediates Endoplasmic Reticulum K+–Ca2+ Exchange to Protect Against Polycystic Kidney Disease
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Background: Prevailing view is that PKD is a ciliopathy. Yet, PC2 is most abundantly expressed in ER. Early studies showed that PC2 is involved in agonist-induced ER Ca2+ release. Decrease in ER Ca2+ release in PC2-deficient cells is believed to contribute to CAMP overproduction and cystogenesis. Recent patch-clamp experiments reveal that PC2 channel is ~40X more selective to K+ than Ca2+, raising the question regarding how PC2 mediates ER Ca2+ release and role of ER-localized PC2 in PKD pathogenesis. To avoid potential polarization impeding ion fluxes, Ca2+ release from ER lumen to cystosol requires coupled counter cation exchange and/or parallel anion movement.

Methods: ER Ca2+ release is assayed by far2 fluorescently stimulated by ATP. PC2-deficient morphant zebrafish and doxycycline-inducible adult-onset PC2-deficient mice are used for in vivo PKD model.

Conclusions: A TP-stimulated ER Ca2+ release is blunted in PC2-null epithelial cells in which expression of WT, but not LOF, PC2 restores ER Ca2+ release. Tricb (trimeric intracellular cation-B) is an ER resident K+ channel mediates K+–Ca2+ exchange for IP3R-mediated Ca2+ release. Expressing WT, but not LOF mutant, Tricb rescues ER Ca2+ release in PC2-null cells. Vice versa, Tricb-null cells have defective ER Ca2+ release, which is rescued by expression of recombinant WT PC2. Zebrafish injected with PC2 antisense morpholin develops dorsal curvature. Co-injecting WT, but not LOF mutant, PC2 RNA rescues defects in PC2-deficient morphant fish. Co-injecting WT, but not LOF, Tricb RNA rescues defects in PC2-null fish. ER targeting of ROMK K+ channel normally expresses on the cell surface rescues Ca2+ release defect and PC2-morphant phenotypes. PC2L1, a PC2 related channel normally expressed on cell membrane and cilia, does not rescue PC2-deficient morphant fish. Transgenic expression of adult-onset kidney-specific Pkd2-inactivated mice ameliorates cystogenesis. Double deletion of Tricb and Pkd2 in mice reveal synergistic genetic interactions.

PO1209

Interactions Between TUL3P3 and ARHL13B in Lipidated Protein Transport to Cilia and Regulation of Renal Cystogenesis
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Background: Signaling outputs from cilia maintain renal tubular homeostasis preventing cystogenesis; however, the ciliary proteins in this process are not well understood. The tubby family protein–TUL3P3 coordinates with the intraflagellar transport
Results: The transmembrane cargos have short motifs that are necessary and sufficient for TULP3-mediated trafficking. We now show that TULP3 is required for transport of the atypical GTPase ARL13B into cilia, and for cilary enrichment of ARL13B-dependent farnesylated and myristoylated proteins. ARL13B transport requires TULP3 binding to IFT-A core but not to phosphoinositides, unlike transmembrane cargo transport that requires binding to both by TULP3. A conserved lysine in TULP3’s tubby domain mediates direct ARL13B binding and trafficking of labelled and transmembrane cargo. We demonstrate that ARL13B helical motors in the palmitoylation site mediates binding to TULP3 and directs trafficking to cilia. TULP3 trafficked labelled cargos are depleted with distinctive temporal kinetics from kidney epithelial cilia during Tulp3 deletion-induced cystogenesis.

Conclusions: We conclude that TULP3 transports transmembrane proteins and ARL13B into cilia by capture of short sequences through a shared tubby domain site. Drugging this interaction domain could provide therapeutics in polycystic kidney disease. The depletion of lipitated cargos with distinct kinetics from kidney epithelial cilia following Tulp3 deletion suggests their differential roles in cilia in regulating renal cystogenesis.

Funding: Other NIH Support - NIGMS, Private Foundation Support

POI1210
Augmented Renal TRPV4 Activity Attenuates Cystogenesis in ARPKD Rats
Kyrylo Pyrshiev, Victor N. Tomilin, Naghmeh Hassanzadeh Khayat, Oleg L. Zaika, Oleh Pochynyuk. The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.

Background: PKD is characterized by development of cysts in the kidney. Abundant evidence suggested that the impaired mechanosensitivity and disturbed [Ca++]i homeostasis are the major determinants of the rate of cystogenesis. ARPKD is caused by missense mutations in fibrocystin. ARL13B is characterized by the development of cysts almost exclusively in the collecting duct. We have previously demonstrated that mechanosensitive Ca++-permeable TRPV4 channel is preferentially expressed in the collecting duct where its activity is imperative for setting resting [Ca++]i levels and mediating flow-dependent [Ca++]i elevations. TRPV4 activity and expression is markedly augmented by high K+ intake, known to increase flow in the collecting duct. Thus, we hypothesized that dietary K+ supplementation would be beneficial in counteracting cystogenesis during ARPKD by stimulating TRPV4-dependent Ca++ influx.

Methods: We used dietary and pharmacological inputs to establish a correlation between the rate of cystogenesis and TRPV4 function in freshly isolated cyst monolayers in a homogenous ARPKD rodent model, PCK43 rats.

Results: We report that treatment of PCK43 rats with high KCI (10%) diet for 1 and 2 months significantly reduced kidney-to-body weight ratio, cystic index, and interstitial fibrosis. We also found a greatly increased total renal TRPV4 expression, channel activity and higher basal [Ca++] levels in native cyst cells compared with respective controls. Importantly, the beneficial effects of high KCI diet were abrogated when PCK43 rats were also treated with the selective TRPV4 inhibitor, GSK2193874. GSK2193874 treatment also exacerbated cystogenesis in control PCK43 rats by modestly increasing kidney-to-body weight ratio. Surprisingly, high K+ alkali diet (10% KClO4/Citrate) also aggravated the disease progression despite augmented renal TRPV4 expression. However, TRPV4-dependent Ca++ fluxes were dramatically suppressed in freshly isolated cyst cell monolayers from high K+ alkali fed rats, which is consistent with impaired TRPV4 activity.

Conclusions: Our experiments establish the direct link between TRPV4 function and cystogenesis during ARPKD. We propose that stimulation of TRPV4-dependent Ca++ influx.

Funding: NIDDK Support

POI1211
The Transcription Factor Tfap2a Maintains the Epithelial Integrity of Renal Collecting Ducts
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Background: The transcriptional regulator Tfap2a is a member of the AP-2 family of transcription factors. In humans, heterozygous mutations of Tfap2a result in branchio-oculo-facial syndrome (BOFS), which is associated with renal anomalies, including dysplastic, absent and multicystic kidneys. In this project, we aimed to elucidate the molecular functions of Tfap2a in the renal collecting duct.

Methods: We used direct in vivo binding, proximity biotinylation and mass spectrometry to map TULP3-cargo interactions. We generated knockouts of Tulp3 and cargoes in kidney epithelial cells stably co-expressing different variants of TULP3 or cargos, respectively. We generated conditional knockout of Tfap2a in mouse kidney nephric mesenchyme. We performed immunofluorescence for lipitated proteins with respect to kidney cystogenesis.

Results: The transmembrane cargos have short motifs that are necessary and sufficient for TULP3-mediated trafficking. We now show that TULP3 is required for transport of the atypical GTPase ARL13B into cilia, and for cilary enrichment of ARL13B-dependent farnesylated and myristoylated proteins. ARL13B transport requires TULP3 binding to IFT-A core but not to phosphoinositides, unlike transmembrane cargo transport that requires binding to both by TULP3. A conserved lysine in TULP3’s tubby domain mediates direct ARL13B binding and trafficking of labelled and transmembrane cargo. We demonstrate that ARL13B helical motors in the palmitoylation site mediates binding to TULP3 and directs trafficking to cilia. TULP3 trafficked labelled cargos are depleted with distinctive temporal kinetics from kidney epithelial cilia during Tulp3 deletion-induced cystogenesis.

Conclusions: We conclude that TULP3 transports transmembrane proteins and ARL13B into cilia by capture of short sequences through a shared tubby domain site. Drugging this interaction domain could provide therapeutics in polycystic kidney disease. The depletion of lipitated cargos with distinct kinetics from kidney epithelial cilia following Tulp3 deletion suggests their differential roles in cilia in regulating renal cystogenesis.

Funding: Other NIH Support - NIGMS, Private Foundation Support

POI1212
Comparative Multiple-Species Analysis of Renal Disease Mutations in HNF1B
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Background: Hepatocyte nuclear factor 1-beta (HNF1B) is a transcription factor involved in various stages of nephrogenesis and maintenance of renal tubular functions. Mutations in HNF1B are the most common monogenic cause for developmental renal disease, yet the underlying pathways affected are not fully understood. By comparative analysis in Xenopus and directly reprogrammed mammalian cells (iRECs) we investigated a patient-specific mutation (R295C) associated with cystic-dysplastic kidneys.

Methods: We used HNF1B to form renal-like organoids from Xenopus explants. In parallel, we analyzed how HNF1B R295C affects nephrogenesis in iRECs. Transcriptional changes were comparatively analyzed in two different species. We confirmed HNF1B target candidates in vivo using CRISPR/Cas9 editing of Xenopus embryos.

Results: We show that HNF1B is not only an essential component in direct reprogramming but can also induce ectopic pronephric tissue in Xenopus ectodermal explants. Changes in the transcriptomic profile demonstrated alterations in specific renal developmental modules and identified novel direct and indirect targets of the transcription factor HNF1B, which are linked to signaling pathways associated with renal morphogenesis, cilia and organic anion transport.

Conclusions: In conclusion, the combined use of directly reprogrammed mammalian cells and Xenopus renal organoid experiments allow us to gain a unique perspective into evolutionary conserved mechanisms of renal development and HNF1B associated kidney disease.

POI1213
Mosaic Inactivation of Pkd1 in Resistance Arteries Leads to Endothelial Dysfunction in Mice
Vivian C. Dourado, Patrizia Dardi, Luciana V. Rossoni, Luiz F. Onuchic. Universidade de Sao Paulo, Sao Paulo, Brazil.

Background: Cardiovascular problems are the leading cause of mortality in autosomal dominant polycystic kidney disease (ADPKD) and hypertension is observed in 50-70% of patients before significant reduction in renal function. The pathogenesis of ADPKD-associated vasculopathy, however, remains largely unclear.

Methods: Menseretic resistance arteries (MRA) of male normotensive non-cystic Pkd1+/- mice (HT) and their non-cystic Pkd1+/- controls (WT) as well as in hypertensive cystic Pkd1-/-Neater mice (CV) and their non-cystic Pkd1-/- controls (NC) were studied. HT and WT animals were analyzed at the ages of 8-12 and 55-60 weeks and had systolic blood pressure (SBP) recorded by tail plethysmography from 15 to 55 weeks of life, while CY and NC mice were analyzed at 8-12 weeks of life. The endothelium-dependent [acetylcholine (Ach) 10-6 M] and -independent relaxation [sodium nitroprusside (SNP) 10-6 M] and norepinephrine (NE, 10-6 M) and -MCI (120 mM)-mediated contraction were assessed in MRA rings by wire myograph. Structural and mechanical parameters (SMP) were evaluated at 55-60 weeks in HT and WT rings using pressure myograph.

Results: At 8-12 weeks, no significant difference in Ach-induced relaxation was observed in MRA between HT and WT mice. CV mice, on the other hand, displayed lower Ach-induced relaxation compared to NC animals (Maximal response: 44.5±7.7 vs 19.9±6.7%; P<0.05), although this parameter was impaired in NC compared to WT (P>0.001). SNP-induced relaxation was similar among groups. The contraction induced by NE did not differ between HT and WT or between the CV and NC mice. At 55-60 weeks, vascular reactivity and SMP did not differ in MRA between HT and WT mice. Interestingly, no difference in SBP was identified between these groups.

Conclusions: Mosaic inactivation of both copies of Pkd1 led to endothelial dysfunction in MRA, a phenotype not induced by Pkd1 haplosufficiency. Aging did not lead to development of hypertension or vascular dysfunction and remodeling in Pkd1-/-haplosufficient mice. While our data suggest that the endothelial abnormality observed in these cystic mice may be a primary dysfunction, current investigation is assessing a potential contribution of chronic hypertension.

Funding: Government Support - Non-U.S.
DCN1,2

Autophagy Inhibition Ameliorates Polycystic Disease

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Background: We published that there is a decrease in autophagy proteins in Pkd1-RC/RC mouse kidneys. Our study aimed to determine the mechanistic role of suppressed autophagy in causing cyst growth using pharmacological and genetic autophagy inhibition.

Methods: Male Pkd1-RC/RC (RC) mice were treated with 2-Deoxycoformycin (2DG) or Chloroquine (CHLQ) from 50-120 d of age. Kidney specific Pkd1 Atg7 double knockout mice were generated by Ksp1.3 Cre-lox recombination. Relative densitometry units (RDU) were determined on immunoblots. Autophagic flux was measured by the change in LC3-II (autophagosomes) +/− Bafilomycin (Baf).

Results: Autophagic flux was present in wild type (WT) and 120 d old RC but suppressed in 150 d old RC kidneys. LC3-II (RDU) +/− Baf was 0.1 vs 0.7 in WT (p<0.01), 0.6 vs 1.0 in 120 d old RC (p=0.05) and 2.4 vs 2.1 (NS) in 150 d old RC. 2DG resulted in a decrease in ATG12-5 complex and suppressed autophagic flux in RC kidneys. LC3-II (RDU) +/− Baf was 0.5 vs 0.8 in VEH (p=0.05), 0.7 vs 0.7 in 2DG (NS). 2DG significantly reduced cyst growth and improved kidney function. Cystic index (%), count +/− 2DG: 7.7 vs 3.7 (p=0.01), 211 vs 161 (p=0.05). BUN (mg/dL) +/− 2DG: 35 vs 27 (p=0.01). Next, RC mice were treated with CHLQ, a specific autophagy inhibitor. CHLQ resulted in suppressed autophagic flux, less PKD and improved kidney function in RC mice. LC3-II (RDU) +/− Baf was 1.2 vs 1.2 (NS) in CHLQ treated kidneys. Cyst index (%), Cyst no +/− CHLQ in RC mice was 15.5 vs 7 (p<0.007), 231 vs 105 (p=0.05). BUN and creatinine (by HPLC) (mg/dL) +/− CHLQ: 41 vs 26 (p<0.05), 2.9 vs 2.3 mg/dL (p<0.05). Next, autophagy was inhibited in PKD kidneys by generating double Pkd1 Atg7 KO mice. The 2 kidney/BW (%) was improved in Pkd1 Atg7 KO vs single Pkd1 KO mice (32 vs 39 p=0.05). Atg7 KO kidneys had a massive increase in p62 indicating a build-up of autophagic cargo. p62 in WT vs Atg7 KO (RDU) 0.1 vs 1.8 p<0.001. Interestingly Atg7 KO kidneys were filled with tertiary lymphoid organs (TLO): large condensed infiltrates of autophagic cargo. p62 in WT vs Atg7 KO (RDU) 0.1 vs 1.8 p<0.001. Next, autophagy was inhibited in PKD kidneys by generating double Pkd1 Atg7 KO mice. The 2 kidney/BW (%) was improved in Pkd1 Atg7 KO vs single Pkd1 KO mice (32 vs 39 p=0.05). Atg7 KO kidneys had a massive increase in p62 indicating a build-up of autophagic cargo. p62 in WT vs Atg7 KO (RDU) 0.1 vs 1.8 p<0.001. Interestingly Atg7 KO kidneys were filled with tertiary lymphoid organs (TLO): large condensed infiltrates of T and B cells. pAMPK+ was increased in Atg7 KO kidneys. AMPK activation is known to reduce PKD.

Conclusions: Both 2DG and CHLQ suppressed autophagic flux in RC kidneys and resulted in less PKD and improved kidney function. Double Pkd1 Atg7 KO mice had significantly lower kidney weight than single Pkd1 KO mice. Both pharmacological and genetic autophagy inhibition resulted in less PKD.

Funding: Veterans Affairs Support, Other U.S. Government Support

POI215

ARL13B Negatively Regulates Kidney Cysts from Within Cilia

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Background: Polycystic kidney disease (PKD) is intricately linked to the primary cilium. Polycystin proteins localize to cilia and loss of cilia leads to renal cysts. PKD mouse models often disrupt ciliary genes, removing both ciliary and cellular pools of the gene products; however, the molecular pathway(s) that drive cyst formation is unknown. ARL13B is a regulatory GTPase highly enriched in cilia due to a Vps4p motif near its C terminus. ARL13B is also localized to extraciliary sites within the cell. In most tissues, complete deletion of ARL13B leads to short cilia but in kidney ARL13B deletion leads to a loss of cilia and kidney cysts. As cilia loss leads to renal cysts, it was impossible to determine whether these cysts were due to the loss of cilia or the loss of ARL13B-dependent signaling in cilia. To determine the specific function of ARL13B within cilia, we needed a genetic tool that would allow us to isolate the cilial function of ARL13B.

Methods: We engineered mice in which we mutated the valine to alanine within ARL13B’s Vps4p cilia-localization motif so the mice express cilia-excluded ARL13B596A from the endogenous locus. ARL13B596A protein retains all known ARL13B biochemical functions, is stably expressed and is undetectable in cilia. We measured renal cysts and cilia phenotypes to functionally characterize the cistic phenotype of cilia-excluded ARL13B596A/+ mice.

Results: ARL13B596A/+ mice are viable and fertile with slowly progressing renal cysts. ARL13B596A/+ mice exhibit no cistic phenotypes and ARL13B596A+/− mice develop cysts at a more rapid rate than ARL13B596A/− mice. We detect cysts in all nephron segments of ARL13B596A/+ mice. Renal epithelia of ARL13B596A/+ mice retain cilia in normal nephrons as well as cistic regions. We cannot maintain these mice on a diet that restricts cyst growth.

Conclusions: Our findings indicate that ARL13B plays a critical role in the ciliary regulation of kidney cystogenesis. These results suggest that ARL13B functions as a negative regulator of renal cysts, specifically from within the cilium. Further studies are ongoing to dissect the mechanism(s) by which ciliary ARL13B regulates kidney cystogenesis.

Funding: NIDDK Support, Other NIH Support - NIGMS

POI216

Tsc Gene locus Disruption and Differences in Renal Epithelial Extracellular Vesicles

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Background: In tuberous sclerosis complex (TSC), Tsc2 mutations are associated with more severe disease manifestations than Tsc1 mutations and the role of extracellular vesicles (EVs) in this context is not yet studied. We report a comparative analysis of EVs derived from isogenic renal cells except for Tsc1 or Tsc2 gene status and hypothesized that in spite of having similar physical characteristics, EVs modulate signaling pathways differently, thus leading to TSC heterogeneity.

Methods: We used mouse inner medullary collecting duct (mIMCD3) cells with the Tsc1 (TIG cells) or Tsc2 (T2J cells) gene disrupted by CRISPR/CAS9 methodology. EVs were isolated from the cell culture media by size-exclusion column chromatography followed by detailed physical and chemical characterization. Physical characterization of EVs was achieved by tunable resistive pulse sensing and dynamic light scattering, electron microscopy, and western blot analyses.

Results: Physical characterization of EVs revealing similar average sizes and zeta potentials (at pH 7.4) for EVs from mIMCD3 (123.5 ± 5.7 nm and –16.3 ± 2.1 mV), TIG cells (113.5 ± 8.3 nm and –19.2 ± 2.7 mV), and T2J cells (127.3 ± 4.9 nm and –20.2 ± 2.1 mV). EVs derived from parental mIMCD3 cells and both mutated cell lines were heterogeneous (90% of EVs < 150 nm) in nature. Immunoblotting detected cilial Hedgehog signaling protein Arl13b; intercellular proteins TSG101 and Alix; and transmembrane proteins CD63, CD9, and CD81. Compared to Tsc2 deletion, Tsc1 deletion cells had reduced EV production and release rates. EVs from Tsc1 mutant cells altered mTORC1, autophagy, and β-catenin pathways differently than EVs from Tsc2-mutated cells. Quantitative PCR analysis revealed the down regulation of miR-212a-3p and miR-99a-5p in EVs from Tsc2-mutated cells compared to EVs from Tsc1-mutant cells.

Conclusions: EV-derived miR-212-3p and miR-99a-5p axes may represent therapeutic targets or biomarkers for TSC disease.

Funding: Other U.S. Government Support
Background: ADPKD is characterized by epithelial proliferation and cyst growth. Metabolic abnormalities have been identified in renal models, but little is known about alterations in metabolic pathways in human ADPKD. We evaluated plasma metabolic profiles in ADPKD subjects prior to and after exposure to tolvaptan (T) as compared to healthy controls to better understand metabolic alterations in ADPKD and potential associations with disease progression and treatment response.

Methods: Plasma samples were collected and analyzed at baseline and month 12 in 100 ADPKD subjects (50 in T and 50 in placebo [P] arms) enrolled in TEMPO 3:4 (NCT010428948). The protein fraction was removed, and the remaining extract split into equal parts for analysis by tandem mass spectrometry and gas chromatography mass spectrometry platforms. Proprietary software (Metabolon, Inc., Durham, NC) matched ions to an in-house library of standards for metabolite identification and quantitation. Forty age- and sex-matched healthy subjects were analyzed as a control group. Linear mixed effect modeling identified associations of metabolites with ADPKD and treatment vs control, height-adjusted total kidney volume (htTKV), Mayo Imaging Classification (MIC), and T vs P.

Results: Baseline metabolic profiles differed between ADPKD and controls, with significant differences in lipid metabolism, TCA cycle, and amino acid metabolism. Baseline MIC 1C, 1D, 1E (vs 1B) were associated with accumulation of the uremic toxin pseudouridine, elevated fatty acid synthesis, and altered tryptophan metabolism, with similar findings when baseline hTKV was analyzed. Threonine, urea, and dimethylsulfone were decreased in T vs P at month 12, as well as other metabolites involved in lipid and amino acid metabolism.

Conclusions: We identified novel associations of amino acids and lipid metabolic pathways with ADPKD vs control and with measures of disease severity (MIC and hTKV). The metabolic profile was differentially affected in T vs P at month 12 of treatment, supporting a role for discovery metabolomics in evaluating response to therapy.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.
Sildenafil Inhibits ADPKD-Derived Cyst Growth in 3D Culture and Induces Apoptosis in the Han/SPRD Cyt+/Cy+ Rat Model of Renal Cyst Disease

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Background: In prior studies we found that human renal cyst cells express high levels of GMP phosphodiesterase 5, 6 and 9 as compared to normal human kidney cells. In breast cancer, inhibition of eGMP phosphodiesterases induces apoptosis. We tested the hypothesis that sildenafil blocks cell proliferation and/or induces apoptosis in cyst epithelia.

Methods: PKD Q0404X cells were grown in Matrigel and treated with vehicle or sildenafil for 7 days. Cyst size was assayed by light microscopy. Differences in cyst area were analyzed by two-way ANOVA. In separate experiments, male cy+/cy+ rats were given either vehicle or sildenafil in their water supply for 7 or 28 days. Kidneys were harvested and apoptosis was assayed by staining with anti-M30, a monoclonal antibody that binds to apoptosis-associated leakage of cytokeratin 18 in epithelial cells.

Results: 3D cultures of PKD Q0404X cells, cultures treated with sildenafil (1, 2 and 4 µg/ml) are significantly smaller than vehicle-treated cultures (p=0.05 for all doses). Further analysis showed that cysts larger than 150 µm3 were not observed in any sildenafil treated cultures. Figure 1 shows M30 staining in sildenafil (20 µg/kg/d) x 7 to 7 treated rats (panel B, red channel merged with the green autofluorescence channel) versus vehicle treated animals. M30 positive cells are found predominantly around cyst lumens. Apoptotic changes in cyst epithelia were also observed in rats treated with sildenafil for 40 days.

Conclusions: Sildenafil inhibits human kidney cyst growth in 3D culture. In male cy+ rats, sildenafil at a dose of 20 µg/kg/d for 7 or 40 days results in apoptosis of cyst epithelia.

Funding: Private Foundation Support

Seven days of sildenafil treatment induces apoptosis in cystic kidneys. Sections stained with anti-cytokeratin 8/18 (red channel). Nuclei are labeled with Hoechst 33342 Green channel is autofluorescence. A: Vehicle treated male rats. Note the absence of cytokeratin 8/18 in B: Vehicle + 20 µg/kg sildenafil treated for 7 days. Arrows point to cytokeratin 8/18 positive (red cytosolic stain) in cyst epithelia.

Mutation Position and Genetic Background Modulate Disease Expression in Pkhd1 Mouse Models

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Background: Multiple Pkhd1 mutant mouse models have been generated by gene-targeting methods (del5-4, del57) or resulted from spontaneous mutations (cy5). When these mutations are homozygous on inbred backgrounds (DBA/2J (D2); C57BL/6 (B6)), there is either no renal cystic disease or very mild dilatation of the PCTs rather than CCDS. A recent ARegPKD report showed that the position of human Pkhd1 mutations correlates with ARPKD kidney and liver disease severity (Burgisser, KJ 2021). In the current study, we examined the impact of age, mutation position, and mixed genetic background on kidney, liver, and pancreatic disease in Pkhd1 mutants.

Methods: D2-Pkhd1Δ5,Δ7; B6-Pkhd1Δ5,Δ7 and B6-Pkhd1Δ10,Δ14 mouse lines. Intercross strategy to generate a suite of F2 mutants on mixed genetic backgrounds (D2.B6).

Results: D2.B6-Pkhd1Δ5,Δ7 mutants expressed both marked dilatation of the CCDS and liver ductal plate malformation (DPM); no pancreatic cysts were observed. Similarly, D2-B6-Pkhd1Δ10,Δ14 compound heterozygotes had occasional dilated DCTs, a marked DPM lesion, and diffuse cyst formation in the pancreatic ducts. The D2-B6-Pkhd1Δ5,Δ7 and D2-B6-Pkhd1Δ10,Δ14 mutants had occasional dilated DCTs, no DPM or pancreatic cysts.

Conclusions: Age, genetic background, and mutation position modulate organ-specific disease expression in Pkhd1 mutants. On the mixed D2.B6 background both cyli and del5-4 aged F2 mutants develop CCD cysts, similar to human Pkhd1 renal disease. Surprisingly, D2.B6-Pkhd1Δ5Δ7/+ mice had minimal kidney pathology and no pancreatic duct cysts, suggesting that genetic background differentially modulates kidney and pancreatic cystic phenotypes. Mice heterozygous or homozygous for the del5Δ7 mutation expressed minimal kidney, liver, or pancreatic cystic changes. Thus, defects at the 3’ end of Pkhd1 appear to have minimal pathobiological impact, that is not influenced by age or the mixed D2.B6 genetic background. These findings will inform our experimental strategies to identify organ-specific Pkhd1 genetic modifiers.

Funding: NIDDK Support, Private Foundation Support

Rab GTase Regulation in Ciliogenesis and Polycystic Kidney Disease

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Background: Primary cilia are sensory organelles with widespread roles in development and epithelial functions. Mutations resulting in dysmorphic cilia and ciliary dysfunction are associated with renal ciliopathies such as polycystic kidney disease (PKD), yet primary cilia remain enigmatic in terms of their molecular and functional characterisation. Rab GTases are master regulators of vesicular trafficking that have been shown to regulate ciliogenesis and cilia composition, with downstream effects on ciliary function and signalling. Rab are therefore poised to vary or modify primary ciliary function, by working in conjunction with key cilia proteins, including those mutated in PKD and other ciliopathies. Hence, we are examining novel roles for Rab GTases in cilia formation and function and Rab13 has been the focus of recent studies.

Methods: Expression of fluorescently tagged, recombinant Rab13 and knockout of endogenous Rab13 were used to assess the roles of Rab13 GTase in ciliogenesis and cilia function in mouse renal epithelial cell lines grown as monolayers and spheroids. Ciliary morphogenesis, cell polarity and growth were assessed by confocal imaging in live and fixed cells, while biochemical approaches were used to test cilia-dependent signalling and associated molecular pathways, along with Rab13 expression, activation and effector functions.

Results: Our data show that Rab13 localises to the primary cilia of mouse kidney cells and Rab13 loss of function affects ciliogenesis in a variety of in vitro and in vivo models including zebrafish embryos. Characterisation of Rab13 knockout epithelial cell lines altered cilia, the perturbation of ciliopathy-associated protein localisation, and the formation of dysmorphic renal spheroids. Rab13 knockout zebrafish embryos display a range of cilia-associated developmental defects and Rab13 expression is diminished in mouse PKD kidneys.

Conclusions: Here we reveal a novel cilia-associated role for Rab13 GTase. Investigating how the genes and molecules that contribute to the cilial landscape is essential to improve knowledge, for potential translation and discovery of new therapeutic approaches for renal ciliopathies including PKD.

Funding: Private Foundation Support, Government Support - Non-U.S.
Efficacy and Adverse Effects of a Novel Mesoscale Nanoparticle-Guided Siroliimus Delivery Strategy in a Phkd1Pck-Rat Model 

PO1227

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Background: Preclinical studies have shown that mTOR inhibition attenuated renal cystic disease progression but it did not improve outcomes in patients with autosomal dominant polycystic kidney disease (ADPKD). This was attributed to the dose limitations in humans due to mTOR inhibitor toxicity. To increase the mTOR inhibition efficacy and reduce its toxicity in renal cystic diseases, we studied mesoscale nanoparticle (MNP)-guided delivery of an mTOR inhibitor, sirolimus (MNP-sirolimus), in Phkd1Pck-RCK rat. We used recently developed MNPs that selectively and with high affinity target the renal tubular epithelium.

Methods: We synthesized Empty-MNPs or MNP-sirolimus and used them in an experiment that resembles seminal pre-clinical studies of tolvaptan, the only FDA-approved ADPKD therapeutic. Newly outbred Phkd1Pck-RCK rats were divided into 3 groups (each N=8-9) and treated for 8 weeks (p22 to p77) with: Empty-MNP (50 mg/kg IV p06 hours), Pre- and post-treatment cyst volumes were assessed by MRI at p21 and p78.

Results: The MNP-sirolimus or Free-sirolimus both inhibited renal mTOR activity in Phkd1Pck-RCK rats. The mean pS6/total S6 ratios were: 7.9 for MNP-sirolimus vs 19.1 for Free-Rapa and 105.1 for Empty-MNP (p<0.001) while total S6 levels did not differ (p=0.806). Similarly, an 8-week mTOR inhibition reduced mean renal cyst volumes: 39.9 mm3 for MNP-sirolimus vs 59.3 mm3 for Free-sirolimus vs 148.4 mm3 for Empty-MNP (overall p=0.011). However, in pairwise comparison with Empty-MNP treatment, this difference was significant only for MNP-sirolimus (p=0.017) while for Free-sirolimus the significance was marginal (p=0.052). The pre-treatment renal cyst volumes at 3 weeks were not significantly different (p=0.720). Among side effects, mTOR inhibition reduced body weight and heart weight (p<0.004); in both cases, their averages were less severely reduced in MNP-sirolimus as compared to Free-sirolimus treated rats.

Conclusions: Together, our studies support the concept that a novel MNP-guided sirolimus delivery increases renal mTOR inhibition and therapeutic efficacy in renal cystic diseases, while reducing systemic toxicity.

Funding: NIDDK Support, Other U.S. Government Support

PO1228

Biomarkers Reflecting Extracellular Matrix Turnover Are Prognostic for Kidney Function Decline in Patients with ADPKD

PO1229

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders in humans and is caused by mutations in the PKD1 and PKD2 genes. The disease is characterized by development and growth of cysts leading to loss of kidney function. Early markers that reflect the progression of kidney disease in ADPKD and is characterized by an impaired turnover of extracellular matrix (ECM). Here, we investigated the association of ECM biomarkers with rate of kidney function decline in patients with ADPKD.

Methods: We measured four markers of ECM turnover in serum and urine from 305 patients with ADPKD from the DIPAK-1 study (NCT01616927): three markers of interstitial collagen turnover (C3M, PRO-C3 and PRO-C6) and one laminin degradation marker reflecting basement membrane turnover (LG1M). The association of the biomarkers with kidney function decline was investigated with a linear mixed model (change in eGFR/year) and logistic regression (decline in eGFR of >30%). Data was log-transformed if appropriate.

Results: All four markers of kidney fibrosis in serum were associated with eGFR at baseline when adjusting for sex, age, height adjusted total kidney volume (htTKV) and PKD mutation in serum (C3M, P<0.05; PRO-C3, P<0.001; PRO-C6, P<0.001; LG1M, P<0.001). In urine, only C3M and PRO-C6 (C3M, P=0.001; PRO-C6, P<0.001) and not PRO-C3 and LG1M (PRO-C3, P=0.07; LG1M, P=0.31) were independently associated with eGFR. Serum C3M (P=0.005) as well as urine PRO-C3 (P=0.001) and PRO-C6 (P=0.001) were associated with the rate of eGFR decline per year when adjusting for age, sex, baseline eGFR, htTKV and PKD mutation. A total of 60 patients had a decline in eGFR of >30% and when adjusting for sex, age, baseline eGFR htTKV and PKD mutation, only serum C3M (HR=1.48, P=0.02) was independently associated with a decline in eGFR of more than 30%.

Conclusions: Serum C3M as well as urinary PRO-C3 and PRO-C6 were associated with the rate of kidney function decline when adjusting for known determinants of disease severity. Also, serum C3M could identify fast progressors (decline in eGFR of >30%). These markers hold promise that components from the ECM may be used as prognostic markers in ADPKD, but should be validated first in an independent ADPKD cohort.

Magnetic Resonance Fingerprinting (MRF) Identifies Potential Imaging Biomarkers for Autosomal Recessive Polycystic Kidney Disease (ARPKD)

PO1229

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Background: Autosomal Recessive Polycystic Kidney Disease (ARPKD) is an important cause of morbidity and mortality in children with chronic kidney disease (CKD). Novel therapies have shown efficacy in ARPKD animal models, but clinical trials in ARPKD patients have not been possible due to the lack of sensitive measures of kidney disease progression. Non-invasive Magnetic Resonance Imaging (MRI) techniques, including novel MRF Fingerprinting (MRF), show promise in addressing this unmet need.

Methods: We used our recently developed MNPs that selectively and with high affinity target the renal tubular epithelium.

Results: Among side effects, mTOR inhibition reduced (overall p=0.011). However, in pairwise comparison with Empty-MNP treatment, this difference was significant only for MNP-sirolimus (p=0.017) while for Free-sirolimus the significance was marginal (p=0.052). The pre-treatment renal cyst volumes at 3 weeks were not significantly different (p=0.720). Among side effects, mTOR inhibition reduced body weight and heart weight (p<0.004); in both cases, their averages were less severely reduced in MNP-sirolimus as compared to Free-sirolimus treated rats.

Conclusions: Together, our studies support the concept that a novel MNP-guided sirolimus delivery increases renal mTOR inhibition and therapeutic efficacy in renal cystic diseases, while reducing systemic toxicity.

Funding: NIDDK Support, Other U.S. Government Support

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Interaction/Modulation of PKD2 by TACAN

PO1230

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Background: TACAN (also named TMEM128A), recently reported as a mechano- and pain-sensing ion channel, is distributed in diverse non-neuronal tissues such as heart, intestine and kidney, which indicates its potential role besides pain sensation. Previous experimental evidence suggests the presence of an interaction between PKD2 and TACAN. In this study, we investigated the physical and functional interaction between the two proteins.

Methods: We employed mutagenesis, molecular cloning, co-immunoprecipitation, immunoblotting, biotinylation, two-electrode voltage clamp in Xenopus oocytes to measure whole-cell currents and patch-clamp in Chinese hamster ovary (CHO) cells to measure single-channel currents.

Results: We found that TACAN is co-localized and in complex with PKD2 in primary cilia of different kidney cell lines and oocytes. Using oocyte expression, we found that TACAN inhibits the channel activity of PKD2 gain-of-function mutant F604P. Using CHO cell expression, we found that TACAN inhibits both wild-type PKD2 and mutant F604P through reducing their single-channel conductance and open probability. Co-expression of TACAN significantly enhanced the sensitivity of PKD2 to stretch. Further, our data showed that while the first and last transmembrane domains (Tm1 and Tm6) of TACAN are involved in interaction with transmembrane domains of PKD2 only the TACAN Tm6 is functionally relevant.

Conclusions: Our study revealed inhibition of PKD2 channel activity through physical TACAN-PKD2 complexing and that TACAN, but not PKD2, mediates mechanosensitivity of the channel complex. Whether and how TACAN participates in the pore formation remains to be determined.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO1231

Suppressed Autophagy Drives Increased Cellular Metabolic Activity in Human ADPKD Cells

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Background: We published that the autophagy phenotype in Pkd1<sup>h</sup>-<sup>h</sup> mouse kidneys is characterized by decreases in crucial autophagic proteins (Cell Signal 2020). We attempt to determine the mechanistic role of suppressed autophagy as it relates to cell metabolism, viability (viability and proliferation) in ADPKD cells.

Methods: Human primary immortalized cultured cells were used: normal renal cortical tubular epithelium (RCTE, Pkd1<sup>+/+</sup>) and ADPKD cyst lining epithelium (9-12, Pkd1<sup>−/−</sup>). To measure autophagic flux, cells were treated with lysosomal inhibitor chloroquine (C) and mCherry LC3 (fluorescence) was measured. MTX assay was used to measure cellular metabolic activity (cell viability and proliferation). Relative densitometry units (RDU) were measured on immunoblots.

Results: There was an increase in MTT and a decrease in AnnV in 9-12 vs RCTE cell types. MTT OD was 0.36 in RCTE vs 0.44 in 9-12 (p<0.001). AnnexinV (AnnV) (% gated) marker of apoptosis, was 67 in RCTE vs 18 in 9-12 (p<0.001). The increase in LC3-II in C was not seen in 9-12 indicating suppressed autophagy and decreased apoptosis. Autophagy inhibition increased with Veh vs. 0.2 with TAT (p<0.001). TAT did not affect AnnV.

Conclusions: In ADPKD cyst lining epithelial cells there is increased MTT, suppressed autophagy flux, and decreased apoptosis. Autophagy inhibition increased with TAT suggesting suppressed autophagy drives increased cellular metabolic activity in ADPKD cells. The effect of autophagy inhibition /induction on cyst growth in vivo merits further study.

Funding: Veterans Affairs Support, Other U.S. Government Support

PO1232

Tsc2 Mutation Induces Renal Tubular Cell Nonafunctional Disease

Prashant C. Cystic Kidney Disease - I

Methods: To understand the diversity of kidney resident macrophages (KRM), we performed single cell RNA sequencing, parabiosis, and fate mapping on kidneys isolated from wild type and transgenic knock-in reporter mice.

Results: Using single cell RNA sequencing, we identified three subpopulations of KRM including one with enriched expression of Ccr2. Using Ccr2-RFP knock-in reporter mice, we confirmed that these resident macrophages were derived from monocyte precursors and preferentially localize to the renal cortex. Based on our single cell RNA sequencing data, we propose that monocytes undergo a series of differentiation steps upon entering the kidney in order to become Ccr2<sup>+</sup> KRM. Levels of single cell data from the main origin for systemic eKlotho suggest that monocytes require Cx3cr1 in order to differentiate into Ccr2<sup>+</sup> KRM. Loss of Cx3cr1 prevented the accumulation of Ccr2<sup>+</sup> KRM and resulted in a skewed macrophage profile that prevented cilia mutant mice from developing severe cystic disease.

Conclusions: Collectively, our data indicate that monocytes undergo a series of differentiation steps upon entering the kidney and require Cx3cr1 for differentiation into pathogenic Ccr2<sup>+</sup> KRM.

Funding: NIDDK Support, Other NIH Support - 2T32AI07051-38, IP20M134973

PO1234

Species-Specific Differences in FPC-CTD Trafficking: Implications for Differential Activation of Intracellular Signaling Pathways

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Background: ARPKD (MIM 213600) is caused by mutations in PKHD1, which encodes FPC. But, orthologous mouse Pkd1 mutants either have no renal cystic disease or very mild PCT dilatation. We previously showed that MYC/Myc is overexpressed in human ARPKD and mouse Cys1<sup>del67</sup> (cypk) kidneys, but not in several Pkd1 mutants. We also showed that expression of the intracellular carboxy-terminus of mouse FPC (mFPC-CTD), but not human (hFPC-CTD), activates the Myc/Myc promoter (APN 2020). The current study focused on: 1) the intracellular trafficking of mFPC-CTD and hFPC-CTD, and 2) activation of the Src/STAT3 signaling pathway, linked to hFPC-CTD (Aurbil 2020), in a mouse Pkd1 mutant lacking FPC-CTD and in the cpl mouse model of ARPKD, with and without Cy-C rescue.

Methods: Comparative immunofluorescence analysis. Immunolabeled mouse ccd (mccd) and human (hccd) cell lines stably expressing mFPC-CTD and hFPC-CTD, respectively. Kidneys from cypk, Cys1-rescued cypk, and Pkd1<sup>h</sup>-<sup>h</sup>del67<sup>+</sup> mutant mice, western blot and immunofluorescence.

Results: FPC-CTD is the least conserved domain, with 55% identity between human-mouse ccdts, compared with 73% identity across the full-length FPC. The CTD is unique, with an AA-sequence not found in other terrestrial vertebrate proteins. In stable cell lines, mFPC-CTD localized to both nuclei and cilia, whereas hFPC-CTD primarily localized to the apical membrane. In non-cystic del67 kidneys (lacking FPC-CTD), pSTAT3<sup>735</sup> and c-Myc were similar to wild-type controls. In cypk kidneys, pSTAT3<sup>735</sup> and c-Myc were upregulated, but their levels in Cys1-rescued cypk kidneys (Liang 2021) were comparable to wild-type.

Conclusions: Differences in intracellular trafficking of mFPC-CTD and hFPC-CTD may explain the species-specific differences in Myc/Myc promoter activation. Distinct subcellular localizations may reflect divergence in the functional evolution of human and mouse FPC-CTD, with mFPC-CTD functioning as a transcriptional activator, whereas hFPC-CTD functions as a membrane-associated signaling regulator of Src-STAT3. Activation of Src-STAT3 signaling and Myc upregulation are signatures of cystic epithelia, suggesting that renoprotective mechanisms in FPC-deficient mouse kidneys may be more protective.

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PO1235

Reduction of Klotho Promotes Cyst Growth and Epigenetic Age Acceleration in ADPKD

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Background: Symptoms of ADPKD vary in severity and age of onset and tend to accelerate quickly in older patients, eventually resulting in kidney failure. eKlotho has been identified as an anti-aging protein, and the kidney is the organ expressing the highest levels of Klotho protein and the main origin for systemic eKlotho. The soluble serum form of eKlotho (extracellular domain of klotho) was found to be decreased in ADPKD patients, however, the role of eKlotho in ADPKD remains unknown.

Methods: To investigate the role and mechanism of eKlotho in ADPKD, we introduced an eKlotho targeted murine model in lineage tracing and cellular induction experiments to understand TSC cystogenesis. For extracellular vesicle (EV) characterization experiments and a cell culture model in EV containment, we used a newly derived targeted murine model in lineage tracing and cellular induction experiments to understand TSC cystogenesis. For EV-producing cells.

Results: Using lineage tracing experiments, we found principal cells undergo clonal differentiation steps upon entering the kidney and require eKlotho for systemic eKlotho to be secreted. In stable cell lines, Myc/MYC (mFPC-CTD), but not human (hFPC-CTD), activates the Myc/Myc promoter (APN 2020). The current study focused on: 1) the intracellular trafficking of mFPC-CTD and hFPC-CTD, and 2) activation of the Src/STAT3 signaling pathway, linked to hFPC-CTD (Aurbil 2020), in a mouse Pkd1 mutant lacking FPC-CTD and in the cpl mouse model of ARPKD, with and without Cy-C rescue.

Conclusions: Differences in intracellular trafficking of mFPC-CTD and hFPC-CTD may explain the species-specific differences in Myc/Myc1 promoter activation. Distinct subcellular localizations may reflect divergence in the functional evolution of human and mouse FPC-CTD, with mFPC-CTD functioning as a transcriptional activator, whereas hFPC-CTD functions as a membrane-associated signaling regulator of Src-STAT3. Activation of Src-STAT3 signaling and Myc upregulation are signatures of cystic epithelia, suggesting that renoprotective mechanisms in FPC-deficient mouse kidneys may be more protective.

Funding: NIDDK Support, Private Foundation Support

PO1213

Exploring the Heterogeneity of Kidney Resident Macrophages Using Single-Cell RNA Sequencing

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Background: Tissue resident macrophages are highly diverse, even when located within the same organ. This heterogeneity is thought to be driven by localization, temporal origin, time in tissue, and niche specific cues. Importantly, these underlying factors likely influence resident macrophage phenotype and function during disease initiation and progression.

Funding: Other U.S. Government Support

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Underline represents presenting author.
Results: We found that full length αKlotho was decreased in collecting duct cells, macrophages, fibroblasts and T/NK immune cells in Pkd1 homoygous kidneys. Transgenic αklotho delayed cyst growth in Pkd1 conditional knockout mice by normalizing the expression of genes associated with a number of diverse functions, including the genes associated with the transitions between collecting duct cell subtypes and genes involved in epithelial-mesenchymal transition. In addition, we found that the genes associated with the epigenetic clock (DNA methylation age) were dysregulated in those cells in cystic kidneys, and that they could be normalized by transgenic αklotho, suggesting that transgenic αklotho might slow down the process of epigenetic age acceleration in cystic kidneys. The dysregulation of the epigenetic age-acceleration genes, ApoE, Cldn4, Mge and Slc38a2, might contribute to PKD pathogenesis and might serve as potential biomarkers for ADPKD. Finally, transgenic αklotho affected a large number of genes associated with metabolic and oxidative signaling, suggesting that αklotho might act by modifying non-ciliated processes to extend the life span of mice.

Conclusions: Reduction of αklotho regulates cyst growth through diverse signaling pathways. Pkd1 mutation accelerates epigenetic age in ADPKD. Transgenic αklotho not only delayed cyst growth but also slowed down epigenetic age acceleration.

Funding: NIDDK Support

PO1236
Mechanistic Interaction Between Cystin and Fibrocystin/Polyductin in Model Cell Lins and cpk/cpk Kidneys
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Background: Cystin/cpk (cpk) mice exhibit ARPKD-like renal phenotype due to a mutation in the Cys1 gene and loss of cystin. ARPKD (MIM 263200) is caused by mutations in PKHD1, encoding FPC. Both cystin and FPC are present in the primary kidney, but no physical interaction has been reported. Using mouse CCD cell lines, we have shown that FPC levels were reduced in cpk cells by 75% relative to wt. Cystin deficiency is specifically linked to FPC reduction and did not affect cilia development, but altered ciliary architecture (ASN 2020). The current study focuses on cellular mechanisms driving FPC reduction in cystin-deficient cells, and the consequences of FPC loss. We noted that FPC is necessary for proper E3 ubiquitin ligase function and consequently cellular proteome management (Kaimori 2017).

Methods: Immortalized wt and cpk mouse CCC cells. Wt and cpk mouse kidneys. siRNA silencing of Cys1, rQ-PCR, western blot, confocal microscopy, morphometry, patch clamp.

Results: Silencing Cystin in wt cells results in a siRNA dose-dependent reduction of both cystin and FPC. Correlative studies showed marked reduction of FPC in cpk kidneys. Similar Pkd1 mRNA levels in wt and cpk, and kidneys implicate FPC regulation at the protein level. Proteasome or lysosome inhibition did not recover FPC, but activation of autophagy further reduced FPC levels, suggesting a role for selective autophagy in FPC removal. Diminished FPC levels lead to E3 ubiquitin ligase defects and reduced polyubiquitination of proteins, necessary for proteome management. In cpk cells, we showed increased membrane retention of the epithelial sodium channel and increased sodium transport.

Conclusions: Our studies provide the first functional link between cystin and FPC in renal epithelial cells. We propose cystin as a gatekeeper for FPC at the base of the cilia and in the E3 ligase complex. In cystin-deficient cells, FPC is continuously degraded leading to dysregulated ubiquitination and altered proteome homeostasis. These data show a mechanistic connection between the renal phenotypes observed in human ARPKD and cpk mice. The recent identification of human CTSI-related ARPKD (Sci Report, in press) highlights the potential significance of the cystin-FPC mechanistic interaction in the complex pathobiology of ARPKD.

Funding: NIDDK Support, Private Foundation Support

PO1237
Tubular Flow Disruption During Cyst Development in Polycystic Kidney Disease
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Background: Polycystic kidney disease is an inherited disorder in which clusters of cysts develop within the kidneys, causing the kidneys to enlarge and lose function. Cyst development can be due to functional changes caused by mutations in ciliary localized proteins Pkd1 and Pkd2 or changes in cilia formation/structure (e.g. i888 mutants). It is currently unknown how cysts impact tubule flow and cilia, or whether flow alterations occur prior to or after cyst formation is initiated.

Methods: We used inducible Cre conditional mutant mouse models with an optical imaging technique to visualize changes in tubular flow at multiple timepoints during cystogenesis in live kidneys. Additionally, we evaluated dextran absorption into proximal tubules as an indicator of tubule flow in mutant and control mice during cyst development. We determined the number of dextran+ proximal tubules in control and mutant kidneys at multiple timepoints during cyst development. This corresponds to a 56.8% of cells that are both dextran+ and LTA+ (proximal tubule) by flow cytometry and similar results were obtained by IF analysis. We also find an increase in resident and infiltrating macrophages around the forming cysts.

Conclusions: The use of intravital imaging approaches allows us to evaluate changes in tubule flow as cysts progress. With the addition of cilia markers, we will examine the responses of the cilium to the changes in flow. Preliminary data suggests that alterations in tubule flow occur at early time points during cyst initiation with larger cysts seldom containing epithelium that are dextran+. These data indicate that loss of tubule flow may be an early event associated with cystogenesis. Our data also suggests that disruption of tubule flow is progressive with fewer tubules with flow at later time points (4-6 months post induction). We are currently assessing whether there is an association between the disruption of flow in a tubule and localized immune responses.

Funding: NIDDK Support

PO1238
FoxM1 Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is driven by mutations in PKD1 and PKD2 genes and is characterized by renal cyst formation, inflammation and fibrosis. Forkhead box protein M1 (FoxM1) is a transcription factor of the Forkhead box (Fox) protein super family which is defined by a conserved winged helix DNA-binding domain. FoxM1 has been reported to promote tumor formation, wound healing and fibrosis in many organs. However, the role and mechanism of FoxM1 in regulation of ADPKD progression is still poorly understood.

Methods: To evaluate the role and mechanisms of FoxM1 in cyst growth in vivo, we treated early stage and long lasting Pkd1 mutant mice with the FoxM1 specific inhibitor, FDL-6. To identify novel FoxM1 target genes involved in cystogenesis, we performed ChIP-sequencing analysis.

Results: We found that FoxM1 was upregulated in cyst-lining epithelial cells in polycystin-1-deficient murine kidneys and human ADPKD kidneys. Inhibition of FoxM1 with FDL-6 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in Pkd1 mutant mice (all p < 0.01). Targeting FoxM1 also decreased renal fibrosis in long last Pkd1 mutant kidneys. Upregulation of FoxM1 promotes cyst growth through: 1) regulation of the expression of Akt and Stat3 and activation of ERK and Rb signaling to increase cystic renal epithelial cell proliferation, 2) inhibition of p65-dependent cystic renal epithelial cell death, 3) facilitation of the recruitment and retention of renal macrophages, and 4) upregulation and activation of fibroblast markers to promote renal fibrosis. In addition, FoxM1-dependent macrophage recruitment was associated with upregulation of monocyte chemotactic protein 1 (MCP-1) and inflammatory cytokine TNFα. Further, we identified novel FoxM1 target genes by ChIP-seq analysis, which may connect FoxM1 signaling to the ciliopathy hypothesis in PKD.

Conclusions: FoxM1 promotes renal cyst growth and fibrosis in ADPKD through Akt, ERK, Rb and STAT3 signaling as well as NF-kB and ciliopathy associated signaling. Targeting FoxM1 in cystic renal epithelial cells may be a viable new therapy for ADPKD.

Funding: NIDDK Support

PO1239
Allosteric Mechanism of PC1 Tethered Agonist-Mediated Signaling
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Background: Polycystin-1 (PC1) is the 11-transmembrane protein product of the human autosomal dominant polycystic kidney disease (ADPKD) gene PKD1. PC1 functions as an atypical GPCR and shares multiple features with the Adhesion GPCRs, including a GPCR autoproteolysis-inducing (GAIN) domain that catalyzes cis-cleavage of the receptors into extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. We previously reported that CTF-mediated signaling to an NFAT promoter-luciferase reporter is dependent on the presence of the stalk, is reduced by ADPKD-associated missense mutations within the stalk, and can be rescued by synthetic, stalk-derived peptides, supporting a tethered ligand mechanism of PC1-G protein signaling (JASN 2018;29:671, JASN 2019;30:882).

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400
Methods: We have combined highly complementary experiments and computer simulations to investigate the mechanism of the tethered agonist-mediated signaling of PC1 CTF. A computer model of the human PC1 CTF was generated using the cryo-EM structure of the PC1-PC2 complex with important missing regions added through I-TASSER homology modeling. All-atom enhanced simulations (1000 ns) using a robust Gaussian accelerated molecular dynamics (GaMD) technique were performed, followed by calculations of residue correlation matrices and free energy profiles. GaMD simulation-predicted residue interactions important for WT stalk-mediated activation of PC1 CTF were validated with newly designed mutation experiments.

Conclusions: Complementary experiments and simulations studies support the function of the PC1 CTF stalk region as a tethered agonist and suggest a mechanism whereby it can induce TOP-pore loop interactions which can be further translated to the GaMD for G protein activation. This heightened knowledge is expected to facilitate future drug design efforts targeting this function of PC1 for more effective treatments of ADPKD.

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PO1240

Abstract Withdrawn

PO1241

Analysis of Calcium Signaling in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Dorien Van Giel,1 Jean-Paul Decuyper,1 Djalila Mekahl,1,2 Rudi Vennekens.1

Background: ADPKD is an inheritable kidney disease characterized by the development of fluid-filled renal cysts, mainly caused by mutations in the PKD1 and PKD2 genes, leading to loss of renal function. Molecular mechanisms underlying cystogenesis are poorly characterized but it is postulated that disturbed calcium homeostasis is a primary event in cystogenesis. The precise molecular players that cause this disturbance are largely poorly explored especially in human cell types. We therefore aim to characterize the profile of calcium-coupled G-protein coupled receptors (GPCRs) in a human renal epithelial cell models, to identify which receptors are present, whether their function is affected in ADPKD and whether they can be used to modulate cyst formation and growth.

Methods: Urine-derived conditionally immortalized proximal tubule epithelial cells (ciPTCs) of ADPKD patients and healthy controls were screened for calcium-coupled GPCRs, using an agonist library on Fura-2 loaded cell populations seeded in a 96-well format. Validation of specific hits was done using single-cell measurements with a fluorescence microscope and built-in perfusion system in the ciPTCs as well as in tissue-derived conditionally immortalized cystic cells (ciCCs). Matrigel-based 3D cell culture was used to grow ciCCs to assess their ability to form cystic structures. Structures were stained with nuclear and cytosolic stains and imaged via confocal microscopy.

Results: From a library of 418 GPCR agonists a selective amount of calcium-coupled GPCRs was found functionally active in ciPTCs. ciPTCs from both healthy controls and ADPKD patients were found to functionally express purinergic -, histamine -, serotonin and dopamine receptors. In single-cell experiments, we did not find any significant differences in functionality between healthy controls and ADPKD patients, but observed that response characteristics are mainly donor-specific, suggesting patient-specific disease mechanisms. ciCCs grown in 3D cell culture were found to form hollow, cell-lined cyst-like structures.

Conclusions: We describe the first thorough characterization of calcium-coupled GPCRs in a human proximal tubule epithelial cell model. We established a 3D cyst growth assay using tissue-derived cystic cells to explore the possibility to use the identified GPCRs to modulate cyst formation and growth.

Funding: Government Support - Non-U.S.

PO1242

Loss of Polycystin Function in Lymphatic Cells Impair CPT1a Expression and Fatty Acid Uptake
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Background: Homozygous Pkdl or Pkd2 null mutant mice die at mid-gestation due to vascular abnormalities including edema and hemorrhage. We have previously shown that edema in Pkd1 and Pkd2 knock out mice is due to abnormal lymphatic morphogenesis, with grossly dilated, blood filled dermal lymphatic vessels. Because proper lymphatic development is supported by fatty acid β-oxidation (FAO), we probed fatty acid transport in Pkd1/Pkd2 lymphatic endothelial cells (LECs).

Methods: Pkd1- and Pkd2- mutant LECs were isolated from mouse E14.5 embryos or generated using lentiviral shRNAs against PKD1 or PKD2 in human dermal LECs (HDLECs). Protein levels of PC1, PC2 and CPT1a were determined by western blotting and CPT1a/CPT2 mRNA levels were analyzed by qRT-PCR. Fatty acid uptake was assessed by BODIPY® 585/596 C12, staining of control and Pkd mutant LECs pre-incubated with or without 50 µM palmitate, and counterstained with mitotracker. Cells were imaged by confocal microscopy and the relative abundance of lipid droplets were quantified using ImageJ software. Each experiment was repeated 3 times and pairs of means (mutant versus control) were compared using Student’s T-test.

Results: Embyronic Pkd1- and Pkd2- murine LECs exhibit a robust decrease of CPT1a protein levels. In addition, CPT1a protein levels were significantly reduced in PKD1 and PKD2 depleted HDLECs, suggesting a conserved role of Pkd1/2 in CPT1a regulation. PC1 and PC2 depletion in HDLECs results in an accumulation of cytoplasmic lipid droplets which often co-localized with mitochondria, indicative of impaired fatty acid utilization. The ability of PKD mutant cells to metabolize fatty acids is further challenged by pre-treatment with 50µM palmitate, which exacerbates the accumulation of lipid droplets.

Conclusions: Our results highly suggest that polycystin function is required to maintain normal levels of CPT1a expression and fatty acid transport to mitochondria in LECs. We thus speculate that a defect in FAO with consequent dysregulation of gene expression is the basis of impaired lymphangiogenesis in Pkd1/2 mutant embryos.

Funding: NIDDK Support

PO1243

Pharmacological Activation of Long-Form PDE4 Enzymes Suppresses Disease Progression in PkdHRC/RC and Pkd1 Knockout (iKspCrePkd1/lox,lox) Mouse Models of ADPKD
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Background: Upregulation of cAMP signaling is thought to promote cystogenesis in ADPKD. Phosphodiesterase 4 (PDE4) enzymes degrade cAMP and contribute to its compartmentalized signaling. We have previously described novel small molecules that allosterically activate long isoforms of PDE4 and lower intracellular cAMP. Here we demonstrate significant efficacy with MR-L22, an advanced PDE4 activator compound, on suppressing cystic burden and preserving kidney health in orthologous models of ADPKD.

Methods: The effects of the long isoform PDE4 activator MR-L22 (administered or vagally) were assessed in rapidly (iKspCre (RC/RC mice) and more effective than vasopressin V2 receptor antagonists.

Results: Compared to vehicle treated controls, MR-L22 treated Pkd1/1 mice exhibited reduced kidney CAMP levels, cystic indices, kidney weight/body weight ratios (Kw/Bw) and MRI measured total kidney volumes (TKV) (Table and Figure). Long isoform PDE4 activation significantly protected kidney function and, when compared to tolvaptan, animals receiving MR-L22 produced significantly less urine volume. MR-L22 also suppressed the aggressive cystic disease exhibited by tamoxifen induced (P10) iKspCrePkd1/lox mice, where Kw/Bw and cystic indices were reduced in comparison to vehicle control (results not shown).

Conclusions: Small-molecule activators of long isoforms of PDE4 suppress cystic disease progression in key translational models of ADPKD and may be better tolerated and more effective than vasopressin V2 receptor antagonists.

Funding: Commercial Support - Miro Ltd

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Underline represents presenting author.
RGLS4326 Increases Urinary PC1 and PC2 Levels in Individuals with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is caused by mutations of either PKD1 or PKD2 genes, leading to reduced function of their respective protein products PC1 and PC2. Both proteins are secreted in exosomes, and their urinary levels inversely correlate with ADPKD severity. RGLS4326, a novel oligonucleotide inhibitor of miR-17, preferentially delivers to kidney tubules and cysts, derepresses miR-17 targets Pkd1 and Pkd2, increases PC1 and PC2, and attenuates cyst growth in multiple PKD mouse models. Whether RGLS4326 treatment would increase PC1 and PC2 in individuals with ADPKD was unknown.

Methods: An open-label, adaptive design, dose-ranging Phase 1b clinical study is ongoing to evaluate RGLS4326 safety, pharmacodynamics and pharmacokinetics in individuals with ADPKD. The study will enroll ~27 patients (9 per cohort) treated subcutaneously with one of three RGLS4326 doses (1, 0.3, and 0.1 or 0.5 mg/kg Q2W x 4 doses) and will be followed for 28 days after the last dose (Day 71). The major inclusion criteria are Mayo Imaging Classification of 1C, 1D, or 1E, and GFR between 30-90 mL/min/1.73 m2. The urinary biomarkers include PC1 and PC2 on exosomes, kidney injury marker 1 (KIM1), and neutrophil gelatinase-associated lipocalin (NGAL).

Results: Nine patients (mean GFR 49 mL/min/1.73 m2, mean age 50 yr) were enrolled in the first cohort; each patient received four doses of 1mg/kg of RGLS4326 Q2W. RGLS4326 was well tolerated with no serious adverse events. PK profiles were similar to healthy volunteers, with a plasma half-life of 9 hours and plasma AUC levels after the first cohort; each patient received four doses of 1mg/kg of RGLS4326 Q2W.

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PO1247

Beneficial Effects of Bempedoic Acid Treatment in ADPKD Mice
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Background: ADPKD has limited therapeutic options. Bempedoic acid (BA), an inhibitor of ATP citrate-lyase (ACLY), FDA-approved for hyperlipidemia, catalyzes a key step in cholesterol synthesis that is important for cell growth and proliferation. BA also activates AMPK in mice. We hypothesized that BA could be a novel ADPKD therapy by inhibiting cyst growth and proliferation and promoting oxidative metabolism via ACLY inhibition and AMPK activation.

Methods: Murine Pkd1-null kidney cell lines derived from either proximal tubule (PT) or collecting duct (IMCD) were grown in Matrigel cultures and treated with BA before cyst analysis by microscopy. In vivo, male and female Pkd1fl/fl, Pkd1fl/C125R, Tg-OR-Cre transgenic C57BL/6 mice were induced with IP doxycycline injection on P10 & 11. Mice were then treated with BA (30 mg/kg/d) ± tolvaptan (30-100 mg/kg/d) by oral gavage from P12-21. As measures of disease severity, total kidney weight to body weight (TKW/BW) and renal BUN were measured. Kidney homogenates were then treated immunoblotted for expression of key disease biomarkers and other relevant cell signaling markers.

Results: BA dramatically inhibited cystic growth in 3D cultures in PT and IMCD Pkd1fl/fl kidney cells. In ADPKD mice, BA reduced TKW/BW vs. vehicle at euthanasia (6.9 vs. 11.9%; P<0.05). Similarly, tolvanat (100 mg/kg/d) reduced TKW/BW to 7.8% vs. vehicle (P<0.05). Addition of BA to tolvanat caused a further reduction in TKW/BW (4.9%; P<0.05) vs. tolvanat alone. BA reduced BUN vs. vehicle (59 vs. 107 mg/dL; P<0.05). Tolvaptan also decreased BUN vs. vehicle at 30 mg/kg/d (68 vs. 86 mg/dL; P>0.05). Again, addition of BA to tolvanat at 30 mg/kg/d caused a further significant reduction in BUN (38; P<0.05). BA reduced ACLY and stimulated AMPK activity in kidneys vs. controls. BA also inhibited mTOR and ERK signaling, which are upregulated in ADPKD. BA also sharply reduced kidney injury markers KIM-1 and, to a lesser extent, NGAL. These BA effects occurred alone and in concert with tolvanat.

Conclusions: BA inhibited cyst growth in vitro and ADPKD severity in vivo. Combined BA and tolvaptan treatment further improved ADPKD outcomes in vivo. BA significantly reduced kidney injury markers and mTOR and ERK signaling. BA may be a promising new ADPKD therapy, having beneficial effects on disease severity when used alone with tolvanat in mice.

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PO1248

Unraveling Fundamental Mechanisms of UMOD Quality Control and Their Role in UMOD-Associated CKD
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Background: UMOD is a GPI-anchored protein expressed in the Thick Ascending Limb of Henle. When properly folded, it transits from the ER to the membrane via the Golgi. Little is known about UMOD’s specific trafficking partners and its quality control mechanisms in the early secretory pathway. Mutations in UMOD disrupt protein folding and promote ER retention, triggering ER-stress pathways and cell death that causes UMOD-associated dominant-tuberous-intestinal kidney disease. It was recently shown that mutant misfolded MUC1-cis is trapped in TME9-containing vesicles and that treatment with compound BRD4780, releases it to the lysosome. We hypothesize that a similar pathogenic quality control mechanism is active in ADTKD-UMOD.

Methods: Co-immunoprecipitation (co-IP) of UMOD and TMED cargo-receptors was assessed in HEK293 cells transfected with wild type (wt) or mutant (C126R) human UMOD. Next, we performed untargeted Affinity Purification Mass Spectrometry followed by tandem MS to generate a list of UMOD interactors. We also conducted in vivo studies in UMODfl/C125R mice.

Results: We identified distinct wt and mutant UMOD interactomes using an unbiased AP-MS proteomics approach. Several interactors, including members of the TMED family, were significantly enriched in the mutant UMOD interactome. Targeted co-IP in lysates of HEK293 cells transfected with UMOD and interacting protein candidates confirmed these results. Proteomics were further characterized, when pulling down TMEDs, we found abundant immature non-glycosylated UMOD, suggesting entrapment in early secretory compartments. In vivo, treatment with BRD4780 was suggestive of disrupted interactions between mutant UMOD and interacting partners responsible for toxic ER-retention and accumulation. Shedding light on these new molecular mechanisms may unmask new therapeutic strategies for the treatment of ADTKD-UMOD.

Funding: Private Foundation Support

PO1249

Restricted Feeding Diet Overrides the Cyst Promoting Effect of Cisplatin-Induced Renal Injury in Both Ifh88 and Pkd2 Mutant Mouse Models
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Background: Multiple renal cystic diseases, including PKD, are caused by dysfunction of the primary cilium. Links between cilia dysfunction, cyst formation, and renal injuries have been reported with evidence showing that injury exacerbated the rate of cyst formation in kidney. In addition, dietary restriction has been reported to ameliorate cyst growth in several PKD animal models. Here we evaluate the effects of both renal injury and dietary restriction on cyst formation in two different cilia-mutant mouse models.

Methods: To test the effect of renal injury on cyst formation, we established an alternative approach to induce chronic renal injury by utilizing a low-dose repeated cisplatin treatment (5.0mg/kg IP; once a week for 4 wks). To evaluate the impact of dietary restriction and renal injury on cyst formation, adult induced conditional Ifh88 and Pkd2 mutant mice were utilized. The study design including cisplatin treatment along with 85 % dietary intakes are shown in Figure 1. Mice were euthanized at 5 wks post last cisplatin injection for analysis. Multiple features including renal injury, proliferation, fibrosis, macrophage accumulation, and cystic index were analyzed.

Results: Low-dose repeated cisplatin treatment resulted in increased Kim1 expression in both Ifh88 and Pkd2 mutant mice compared to controls. Analysis of the cystic phenotype showed that there was a significant increase in cyst formation in mutant mice after cisplatin compared to saline-treated group and the location of cysts corresponded to the injured regions. Interestingly, the rapid cyst formation in cisplatin-treated kidneys was ameliorated when the mice were on the restricted diet (Figure 1). More importantly, kidneys from mice with restricted feeding displayed decreased levels of proliferation, fibrosis, macrophage accumulation, and cystic index were analyzed.

Conclusions: These data show that low-dose repeated cisplatin treatment could be used as an alternative approach to IRI to accelerate cyst formation in both ifh88 and pkd2 mutant models. More importantly, it suggests that cyst progression associated with injury to cystic kidney disease could be ameliorated through dietary interventions.

Funding: NIDDK Support

PO1250

Peroxisomes Are Dispensable for Normal Renal Function
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Background: Peroxisomes are single membrane-bound cellular organelles identified in the kidney in 1954. Peroxisomes are ubiquitously present in eucaryotic cells with highest abundance in renal proximal tubule cells and hepatocytes. The variety of metabolic and antioxidant functions in which peroxisomes are involved is highlighted by human mutations in PEX genes encoding peroxisomal proteins required for proper peroxisome biogenesis. Hence, the complete loss of peroxisomes causes Zellweger’s spectrum disorders (ZSD), devastating multiorgan failure which include renal impairment. However, the (patho)physiological role of peroxisomes in the kidney remains unknown.

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Methods: Here we addressed the role of peroxisomes in renal function in male and female adult rats with conditional ablation of Pex5-driven peroxisome biogenesis in the renal tubule (cKO mice).

Results: Functional and histological analyses of both infant and adult cKO mice did not reveal any overt kidney phenotype. However, male cKO mice exhibited substantial reduction in kidney weight and body weight ratio. Stereological analysis of electronic microscopy results showed a complete absence of peroxisomes accompanied by increase in the number and in the volume of mitochondria in proximal tubule cells of cKO mice. Integrated deep transcriptome-sequencing and metabolome analyses revealed profound reprogramming of a great number of metabolites, including upregulation of different classes of steroids, such as plasmalogens and sphingomyelins (two major classes of membrane lipids) and the metabolism of glutathione. Although this analysis suggested compensated oxidative stress, four weeks of high fat feeding challenging the ability of proximal tubule cells to metabolize lipids significantly increased mitochondrial dysfunction.

Conclusions: We demonstrate that renal tubular peroxisomes are dispensable for normal renal function. This indicates a large flexibility of proximal tubule cells both in terms of lipid membrane composition and metabolic/antioxidant functions. Our data also suggest that renal impairments in ZSD patients are of extrarenal origin.

Funding: Government Support - Non-U.S.

PO1251
Weight Loss to Slow Cyst Growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Background: Recent studies in animal models of ADPKD support that food restriction can profoundly slow cyst growth and maintain renal function. We have also reported that overweight and obesity are strong independent predictors of ADPKD progression. Thus, it is plausible that weight loss, caloric restriction, and/or periods of fasting may slow ADPKD progression in humans; however, the feasibility of these dietary interventions, and whether the driver of therapeutic efficacy is periods of fasting or reduction in body weight, is unknown.

Methods: We conducted a one-year study evaluating feasibility of delivery of a behavioral weight loss intervention based on either daily caloric restriction (DCR) or intermittent fasting (IFM) in adults with overweight/obesity, ADPKD, and eGFR ≥30 m/min/1.73m2 (targeted weekly energy deficit of ~34% in both groups). We also evaluated the safety, acceptability, and tolerability of each intervention, and obtained exploratory insight into changes height-corrected total kidney volume (htTKV).

Results: 28 participants (16F/12M; average age 40.9 yrs, average BMI 34.7 kg/m², eGFR of 69±23 m/min/1.73m²) were randomized to either DCR (n=15) or IFM (n=13).

- Clinical significance: (~5%) weight loss was achieved in both groups at month 3 (DCR: -7.1±4.2%; IFM: -5.5±3.3%). At 12 months DCR lost additional weight while weight loss in IFM plateaued (DCR: -9.1±6.0%; IFM: 4.9±5.6%; p<0.05 DCR vs. IFM).

- DCR had a more favorable safety, tolerability, and adherence profile than IFM. Annual htTKV %Δ was qualitatively low in both groups in comparison to histological data, despite comparable clinical characteristics (DCR: 1.5±3.4%; IFM: 1.7±6.1%). Annual htTKV %Δ was highly correlated with %Δ in weight (r = 0.68, p<0.001). Abdominal saturated adipose tissue (SAT), visceral adipose tissue (VAT) and total adipose tissue (TAT) quantified by MRI were all reduced at one year (p<0.05). Change in VAT (r = 0.49, p<0.05) and TAT (r = 0.46, p<0.05) also correlated with annual htTKV %Δ.

- Conclusions: DCR, and particularly DCR, were feasible interventions over a one-year period in adults with ADPKD and overweight/obesity and showed favorable effects on kidney weight as compared to historical controls, supporting conduction of a phase II randomized controlled trial.

Funding: NIDDK Support, Private Foundation Support

PO1252
Social Determinants of Health (SDOH) and Healthcare Resource Utilization (HRU) in Autosomal Dominant Polycystic Kidney Disease (ADPKD) by CKD Stage
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Background: SDOH contribute to health disparities in CKD. This study describes SDOH and HRU among ADPKD patients with commercial (COM) insurance compared to a lower income managed Medicaid (MM) population.

Methods: The study included 8,766 COM and 5,416 MM patients from a national claims database. Patients had ≥2 ADPKD diagnoses between 7/1/2016- 12/31/2018 and were continuously enrolled in the study period. Patients were linked to SDOH by 9-digit ZIP address providing a precise assignment compared to Census data. HRU included inpatient days and emergency room (ER) visits per 1000 patients per month (PPPM) over 1-year follow-up.

Results: COM patients were more likely to be female (60% vs 54% COM) and on average 8 years younger. MM patients had 1.3x higher Charlson Comorbidity Index (CCI) scores, 40% lower income, were 2x more likely to live below federal poverty level, 1.3x less likely to complete high school, 2.7x more likely to speak English not well or at all, 2.6x less likely to own a vehicle, 53% more likely to be unemployed, and lived in a poverty stricken census tract. Social determinants of health such as healthcare access area 6.8%-6.4% more often. The differences between payers were consistent across CKD stages, except CCI scores increased with higher CKD stage for both groups. Disparities in income, unemployment rates and provider shortages tended to increase with CKD stage. Mean bed days ranged from 34.6 (Stage 1) to 402 (Stage 5), and ER visits PPPM ranged from 38 to 114 for COM and 154 to 376 for MM. Hospital readmissions and use of post-acute care were high in both groups, with 15% of COM and 20% of MM readmitted within 30-days of inpatient admission. Median annual % increase in total charges was 25%-35% MM having at least one PAC stay during follow-up. HRU increased with CKD stage.

Conclusions: ADPKD patients have large variation in SDOH by type of insurance. Lower social status of MM patients may be associated with higher HRU, and these differences likely relate to increased healthcare and social service progresses. In the clinical care of this vulnerable population, consideration of SDOH such as language barriers, transportation insecurity, and poverty is recommended.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

PO1254
Overweight and Obesity Predict Kidney Growth in Children and Young Adults with ADPKD
Cortney Steele, Zhiying You, Heather Farmer-Bailey, Berenice Y. Gitomer, Michel Chonchol, Kristen L. Nowak. University of Colorado - Anschutz Medical Campus, Aurora, CO.

Background: We have previously reported that overweight and obesity are independently associated with more rapid progression in adults with early-stage autosomal dominant polycystic kidney disease (ADPKD). We now evaluate whether overweight and obesity are also associated with faster kidney growth in children and young adults with ADPKD.

Methods: 54 non-diabetic children and young adults (6-25 years of age) with ADPKD and estimated glomerular filtration rate (eGFR) >80 ml/min/1.73m2 who participated in a 1-year controlled trial. Patients were categorized based on BMI (if <18 years; n=27) or BMI percent for age, sex, and height (if ≥18 years; n=27) as normal weight (n=40 [74%]) or overweight/obese (n=14 [26%]). The longitudinal (1-yr) association of overweight/obesity with change in height-corrected total kidney volume (htTKV) by magnetic resonance imaging was evaluated using multinomial logistic regression models.

Results: Mean±sd. age was 18±5 years, annual % change in htTKV was 6.1±9.0%, and eGFR (full-age spectrum equation) was 112±18 ml/min/1.73m2. The annual % change in htTKV was 5.5±9.1% in the normal weight participants and 7.9±8.6% in overweight/
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POI1255

Metabolomic Changes over 1 Year Following Drug or Lifestyle Interventions in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease. Studies have shown differences in metabolomic profiles in those with ADPKD; however few studies assess change over time.

Methods: We performed metabolomics to assess patterns of change across four groups of participants with ADPKD pooled from 2 randomized clinical trials: placebo control (CON), metformin (1,000 mg/day) (MET), intermittent fasting (IMF; 3 day/ wk of 80% energy restriction from baseline weight maintenance requirements), and daily caloric interventions. Further changes are depicted in Figure 1.

Results: Baseline characteristics for each trial included CON (n=22, 14 female (F), 49±7 yrs of age (means±s.d.), estimated glomerular filtration rate [eGFR] 73±13 ml/min/1.73m², body mass index (BMI) 29±3.4 kg/m²), MET (n=22, 14 F, 48±7 yrs of age, eGFR 69±14 ml/min/1.73m², BMI 29±7.7 kg/m²), IMF (n=10, 5 F, 47±6 yrs of age, eGFR 77±16 ml/min/1.73m², BMI 34±6.5 kg/m²), and DCR (n=9, 5 F, 46±13 yrs of age, eGFR 68±21 ml/min/1.73m², BMI 34±1.5 kg/m²). Age and eGFR did not differ between groups. BMI was higher in the IMF compared to CON (p=0.031). Metabolite changes are depicted in Figure 1.

Conclusions: There are changes at one year in metabolites in adults with ADPKD between control, metformin, intermittent fasting, and daily caloric interventions. Further research is needed to identify metabolomic profile shifts involving drug and dietary interventions.

Funding: NIDDK Support, Other U.S. Government Support

POI1256

Identification of CLC-5, the Electrogenic 2Cl-/H+ Exchanger, as the Dominant Apical Chloride Secretory Transporter in Kidney Cyst Epithelium in Tuberous Sclerosis
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Background: Cyst expansion in Tuberous Sclerosis Complex (TSC) or PKD requires secretion of chloride into the cyst lumen as the driving mechanism for salt accumulation. In PKD, Cl secretion into the cyst lumen is mediated via the eAMP/PKA-stimulation of CFTR in principal cells consequent to the V2 receptor activation by AVP. Kidney cystogenesis in TSC differs from PKD in that cyst epithelia in TSC is comprised of genotypically normal A-intercalated cells, which do not exhibit noticeable expression of either CFTR or the V2 receptor. The identity of the Cl secreting molecule(s) in TSC cyst epithelia remains unknown. Based on RNA Seq analysis in kidneys of Tsc1 KO mice, we hypothesized that the chloride transporter CLC-5 is expressed on the apical membrane of A-intercalated cells in cyst epithelia of humans and animal models of TSC. CLC-5 is a 2Cl-/H+ exchanger that is located in collecting duct A-intercalated cells where it is predominantly localized to endosomes and plays a critical role in dissipating H+ secretion and membrane depolarization by H+-ATPase. This allows parallel movement of Cl and H+ into the endosomes.

Methods: Double immunofluorescence studies utilizing CLC-5 and H-ATPase antibodies were performed on kidney tissue from mice with principal cell inactivation of Tsc1 (Tsc1-Agon2 Cre), p-p.eptide inactivation of Tsc1 (Tsc/Remr Cre), principal cell inactivation of Tsc2 (Tsc2-Agon2 Cre), global heterozygous Tsc2(Tsc2+/−) and cysts from TSC patients.

Results: Double immunofluorescence labeling demonstrated remarkable colocalization of CLC-5 and H-ATPase on apical membranes of an overwhelming numbers of cyst epithelial cells in all models of TSC, including the human kidney cysts. In contrast, kidney cysts in Pkd1 mutant mice showed no apical CIC-5 expression and very few H-ATPase expressing cells.

Conclusions: These are the first reports on apical membrane localization of CLC-5 in A-intercalated cells in any disease state, and suggest that similar to late endosomes/lysosomes, CLC-5 and H-ATPase may function synergistically on cyst epithelia by secreting Cl and H+ into the cyst lumen. These results strongly point to enhanced translocation of CLC-5 and H-ATPase from late endosomes/lysosomes to the apical membrane of cyst epithelia in TSC.

Funding: Veterans Affairs Support, Other U.S. Government Support, Private Foundation Support

POI1257

Two Years In: The Development and Basic Characteristics of a National Patient-Powered Registry in ADPKD
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Background: The therapeutic pipeline in autosomal dominant polycystic kidney disease (ADPKD) has grown, generating a need for more patient participation in clinical trials. To facilitate US ADPKD patient enrollment and to encourage the utilization of patient-reported outcomes in trial design, the PKD Foundation (PKDF) designed a national ADPKD Registry.

Methods: The ADPKD Registry is hosted on a secure, online platform (IQVIA, oc-meridian.com/pkdeare). Participants are consented through the online system and complete a series of modules. The Core Questionnaire includes diagnosis, latest kidney function tests, and comorbidities. Family history, diet and lifestyle, quality of life, and complications of liver cysts, and vascular outcomes are queried.

Results: Between 9/4/19 and 5/1/21, 1,580 ADPKD patients have registered and completed the Core Questionnaire. Participants have a median age of 49 years, 73% have not reached ESKD, and 79% reported a family history of the disease. Currently, the cohort is 71% female, 93% Caucasian, 4.8% Hispanic/Latino and 2.5% African American. Strategic efforts are in development to increase diversity in the cohort. Nearly three quarters of participants had not previously participated in research, with only 27% indicating that they had been in another PKD study or clinical trial. All participants have consented to be contacted about future studies. Many will likely qualify for ongoing trials based on completed module data. Thus far, the Registry platform has made over 2,200 participant contacts regarding six clinical studies, with some individual overlap due to similar eligibility criteria.

Conclusions: The ADPKD Registry is a longitudinal research tool intended to capture ADPKD patient-reported data and is designed to impact research in multiple ways. It will allow for a range of outcomes in ADPKD from early disease through dialysis and post-transplant outcomes. Additionally, modules on health care access & utilization and COVID-19 impact will help the PKDF better understand the challenges of this community.

Funding: Private Foundation Support

POI1258

Polycystic Kidney Disease and Race
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Background: Racial/ethnic differences in the development of kidney failure (ESKD) and transplant (TX) access are well-documented. ESKD is anticipated in familial autonomic polycystic adenomatous polycystic kidney disease (ADPKD), providing the opportunity for greater ESKD preparation. We sought to define the impact of race on ESKD/TX outcomes in ADPKD.
Methods: White (W), African-American (A), or Hispanic (H) ADPKD patients were identified in USRDS 1(2000-6/2018); demographic and laboratory data were obtained. Median income was derived from US Census. Models included: age at ESKD (linear), pre-emptive TX (logistic), and TX after dialysis initiation (Cox), adjusted for age, sex, albumin, hemoglobin, eGFR, insurance, income, ESKD Network, and employment, with W as referent.

Results: Among 41,485 patients, (77.3% W, 13.3% A, 9.4% H), characteristics/outcomes are shown in Table 1. AA and H had lower median income and less private insurance, pre-ESKD nephrology care, and employment. For AA and H, peritoneal dialysis and TX were less common than in W. Albumin, hemoglobin, and GFR were lowest in A. ESKD occurred 2.2 ± 0.2 and 4.8 ± 0.3 years earlier in A and H, compared to W. Adjusted odds of pre-emptive TX were 0.38(0.33, 0.42) and 0.47(0.40, 0.55) for A and H. Adjusted hazards for TX after dialysis initiation were 0.60(0.55, 0.65) for A and 0.78(0.72, 0.85) for H, P<0.001 for all TX rates for A vs W by network are shown in Figure 1.

Conclusions: Despite the hereditary nature of ADPKD, renal outcomes differed by race, attributed to in part, economic and geographic factors. Health inequity is a contributing factor to patient outcomes in ADPKD that needs to be addressed.

PO1260
Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Background: Clinical manifestations of autosomal dominant polycystic kidney disease (ADPKD) can begin in childhood, including evidence of vascular dysfunction, an important predictor of cardiovascular events and mortality. Curcumin is a polyphenol found in turmeric that reduces vascular dysfunction in rodent models and humans free from ADPKD. It also slows kidney cystic progression in a murine model of ADPKD.

Methods: We hypothesized that curcumin supplementation would reduce vascular dysfunction (brachial arterial flow-mediated dilation [FMD]) and aortic pulse-wave velocity (PWV) in children and young adults with ADPKD. In a prospective, randomized, controlled, double-blind trial, n=68 participants 6-25 years of age with ADPKD and an estimated glomerular filtration rate >80 mL/min/1.73 m² were randomized to receive either curcumin supplementation (25 mg/kg body weight/day) or placebo administered in powder form for 12 months. We also assessed change in circulating and urine biomarkers of oxidative stress/inflammation and kidney function. Participants with baseline PWV ≥120 cm/sec were excluded from the aortic PWV analysis.

Results: Seven participants completed the trial. Participants were 18±5 (means±d.) years, 55% female, and 85% non-Hispanic White. The co-primary endpoint, FMD (%), did not change in the curcumin group (baseline: 9.4±4.1; 12-months: 10.6±3.9, compared to the placebo group (baseline: 8.9±4.0; 12-months: 9.3±4.5; p=0.01), and the other co-primary endpoint, APWV (cm/sec) was 51.7±12.0; 12-months: 51.7±8.1; placebo: baseline: 51.8±8.2 cm/sec; 12-months: 52.5±9.5 cm/sec; p=0.53). There was no curcumin specific reduction in vascular oxidative stress, nor any changes in mechanistic biomarkers. hTrkV also did not change over the 12-month study with curcumin administration as compared to placebo.

Conclusions: Curcumin supplementation does not reduce vascular dysfunction or slow kidney growth in children/young adults with ADPKD.

Funding: NIDDK Support, Commercial Support - Verdure Sciences (study drug), Private Foundation Support.

PO1261
Polycystic Kidney Disease Associates with Increased Myopia and Retinal Breaks

Background: Ophthalmologic manifestations in Polycystic Kidney Disease (PKD) are not well known.

Methods: We conducted a retrospective cohort study using EMR data extraction. All adult patients with polycystic kidney disease (“PKD”) and CKD from another cause (“non-PKD/CKD”), seen at our center between 1/1/2000-4/30/2020, and Eye disorders of interest in these 2 cohorts were identified using ICD-9/10 diagnostic codes. The date of the first visit to Nephrology clinic was regarded as “Index date”. The prevalence of Eye disorders at the index date was compared between “PKD” and “non-PKD CKD” cohorts.

Results: A total of 839 patients with “PKD” and 8309 patients with “non-PKD-CKD” were included. Majority of patients in both groups were male (58% [498] and 54% [4457]) and identified as White (88% [758] and 86% [7185]). At the index date, PKD patients were younger (mean age 55 vs 60 years in non-PKD/CKD; p=0.01) and had shorter follow up time (median 901 vs 1311 days; p=0.01). PKD patients had higher eGFR (52 [31-81]; N=795) vs 43 mL/min/1.73m² [29-59; N=3742; p<0.01] and lower prevalence of diabetes mellitus at the index date (23% [198] vs 39% [3270]; p=0.01). Hypertension prevalence was similar between the two groups (91% [778] and 90% [7444]). Myopia and all Retinal breaks (with or without detachment) were found to be more common in PKD as compared to non-PKD CKD after multivariable adjustment for age, gender, race, diabetes and follow up time (adjusted odds ratio 1.4 [95% CI: 1.1-1.7] and 1.7 [1.2-2.8]; respectively; p<0.01). Retinal breaks with detachments by themselves were also more frequent in PKD but did not reach statistical significance (Table). Peripheral retinal degeneration was similar between the two groups.
PO1264
The Impact of Salt Deficiency on Acid-Base Homeostasis in Autosomal Recessive Polycystic Kidney Disease
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Background: In healthy subjects, dietary salt restriction exacerbales imbalances of acid-base homeostasis. The disease progression of autosomal dominant PKD is associated with decreasing serum bicarbonate levels and metabolic acidosis, however very little is known about acid-base imbalance in autosomal recessive (AR) PKD, particularly, in response to dietary restrictions. Here we hypothesized that a salt-deficient (SD) diet leads to electrolytic and acid-base imbalance in ARPKD.

Methods: Male and female PCK/CrlCrjPhd1pck/CRL (PCK) rats were fed a SD (0.01% NaCl, Deyts Inc) diet for 1, 3, 5, 7 and 9 weeks beginning at 4 weeks of age. Before each endpoint, urine was collected, and plasma and tissue samples were harvested. Plasma and urine creatinine, sodium and electrolytes, BUN, and plasma aldosterone levels were measured. Cystic index was defined using ImageJ. Statistical analysis was performed with 2-way ANOVA.

Results: Rats of both genders showed over the course of the SD diet in both sexes. Plasma Na+ and Cl− as well as creatinine increased; and BUN did not change. Plasma aldosterone increased from week 1 to week 5 (week 1: 2.6±1.5 mg/dL, week 5: 10.5±1.5 mg/dL) and 7.7±1.1 (F, p<0.001 (over time)), followed by a return to baseline by week 9 of the SD treatment. These results were significant in cystogenesis in female rats from week 1 to week 9 of the SD diet (week 1: 14.2±1.9%, week 9: 36.3±2.4%). Further, we observed an increase in plasma pH (week 1: 6.98±0.08 (M) and 6.83±0.03 (F), week 7: 7.16±0.08 (M) and 7.13±0.02 (F) (p<0.001 (over time)) and a decline in urine pH (week 1: 7.69±0.42 (M) and 8.75±0.06 (F), week 7: 5.80±0.07 (M) and 5.72±0.08 (F), p<0.001 (over time)) in both sexes throughout the dietary challenge.

Conclusions: PKC rats on a SD diet exhibit acidification of urine pH and an increase in plasma pH. We can speculate that acid base transporters such as NHE1, NBCe2, and pendrin are upregulated to conserve plasma sodium leading to a shift in acid-base homeostasis. Further studies aimed at elucidating the role of these transporters may add to the current knowledge regarding the pathogenesis and dietary management of ARPKD.

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PO1265
A Combination Therapy with Two Dietary Supplements Acting on Different Mechanisms Ameliorates Disease Progression in a Rat Model of Polycystic Kidney Disease

Background: Recently, our lab reported that dietary interventions to induce ketosis ameliorate disease progression PKD animal models, and that this effect involves the natural ketone beta-hydroxybutyrate (BHB). Additionally, we have recently shown that renal microcrystals exacerbate disease progression in PKD models. We now show that a combination of citrate and BHB effectively inhibits PKD progression. These compounds act on separate mechanisms, synergistically preventing cyst formation and cyst growth in young rats. In adult rats, the combination treatment leads to a partial reversal of existing renal cystic disease.

Methods: Juvenile and adult male and female PCK rats were treated with BHB, citrate or in combination via drinking water for 5 or 4 weeks respectively, then sacrificed and analyzed for changes in cystic burden and markers of disease progression. Additionally, rats were placed in metabolic cages to assess changes in urine parameters.

Results: Administration of either BHB or citrate alone in the drinking water effectively ameliorates PKD progression in a rat model. Combining BHB and citrate produced a synergistic effect. Cystogenisis and cyst growth were inhibited in juvenile animals. In adult animals with pre-existing renal cystic disease, the treatment leads to TSC2 disease regression. We also found that administration of excess sodium and potassium alone, at doses that would be provided from the salts of citrate and BHB, lead to a worsening of PKD in our rat model.

Conclusions: The beneficial effects of ketosis are mimicked by administration of BHB in the drinking water and are consistent with a number of groups findings suggesting an underlying metabolic defect in PKD. Our other recent findings suggest excessive renal crystal burden leads to accelerated disease progression in PKD models. Renal cystal formation can be prevented by administration of citrate to both chelate calcium and raise urinary pH. These results are of high clinical significance because BHB and citrate
are widely available and classified as safe dietary supplements. These results suggest that a combination of widely available and generally safe dietary supplements, when appropriately formulated, demonstrate high promise for supporting kidney health in PKD.

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**PO1266**

A Single-Center Experience of ARPKD in Adults

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**Background:** Autosomal recessive polycystic kidney disease (ARPKD) is an inherited ciliopathy with 50% presenting with enlarged kidneys in utero or early infancy. ARPKD has an incidence of ~1:20,000 live births and arises from biallelic variants in \( PKHD1 \) encoding for fibrocystin, with variants in \( DZIP1L \) accounting for <1% cases. Imaging findings include large echogenic kidneys, poor cortico-medullary differentiation, renal cysts or "salt and pepper appearance". ARPKD-congenital hepatic fibrosis (ARPKD-CHF) complex consists of renal disease with biliary dilatation portal hypertension and splenomegaly. 50% develop ESRD in childhood with limited data on renal prognosis for those that present later.

**Methods:** A retrospective chart review of patients >16 yr of age with cystic kidney disease and/or congenital hepatic fibrosis to identify possible cases of ARPKD. Clinical phenotype (compatible hepato-biliary and renal involvement) and/or genetic testing were used to verify the diagnosis.

**Results:** We identified 29 patients with ARPKD-CHF, out of which 13 ≥16 yr (mean 32.4 yr). 38% were males, 15% identified as Hispanic and the rest as non-Hispanic whites. All had radiographic evidence of renal and/or hepato-biliary involvement and 5 of 13 patients had biallelic variants in \( PKHD1 \). On the most recent imaging study, 92% had renal cysts, 23% large echogenic kidneys, 23% poor renal corticomedullary differentiation, 15% medullary sponge kidney, 23% with salt and pepper pattern. Only 3 of 13 (23%) had reached ESRD or received a kidney transplant, while the remaining had a mean eGFR of 46ml/min/1.73m\(^2\). Of these, 50% had eGFR ≥60ml/min/1.73m\(^2\). Amongst those with hepato-biliary involvement, 40% had CHF, 53% portal hypertension, 40% splenomegaly, 26% liver cysts.

**Conclusions:** We describe a cohort of patients with ARPKD, the majority presenting as adults, with an eGFR ≥60ml/min/1.73m\(^2\). A significant number of these patients had multiple large renal cysts. Absence of obvious renal phenotype in patients with congenital kidney anomalies. Application of the SMV pipeline may increase diagnostic rate of the cohort to 22.5%.

**PO1267**

Analysis of Somatic Mosaic Mutations in Nephropathy-Associated Genes Reveal Candidate Disease-Causing Mutations in Previously Germ-line-Negative Cases


**Background:** Somatic mosaicism variant (SMV) arises due to postzygotic mutations that result in two genetically distinct populations of cells in the same person. SMVs may be missed by standard search for germline (or inherited) mutations, and the use of dedicated analytic pipelines for SMVs can potentially explain "exome negative" cases. Somatic mutations were identified through GATK Mutect2 software, and clinically annotated following the American College of Medical Genetics and Genomics (ACMG) guidelines. We focused on the analysis of 625 nephropathy-associated genes previously used for the germline analysis.

**Results:** Previous analyses germline variants had identified 52 diagnostic variants in this cohort (20.9% diagnostic rate). In addition, the SMV pipeline identified candidate disease-related SMVs in 4 "exome-negative" patients (1.6% of cases). The SMVs were detected in \( RET, EGF \) and \( COL4A5 \), and are reported in Table 1. This improved the diagnostic rate of the cohort to 22.5%.

**Conclusions:** Analyses of somatic mosaic variants can increase diagnostic yield in patients with congenital kidney anomalies. Application of the SMV pipeline may increase diagnostic in other forms of kidney disease.

**PO1268**

Comparison of Imaging Approaches for Quantifying Total Kidney Volume (TKV) and Fibrosis in a Mouse Model of Polycystic Kidney Disease (PKD)

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**Background:** 3D imaging and histology are critical tools for assessing PKD in patients and animal models. Magnetic resonance (MR) imaging provides resolution, but is time consuming, expensive, and access to equipment and expertise is limiting. Robotic ultrasound (US) imaging is lower resolution but fast. Similarly, picrosirius red (PR) staining and standard light microscopy is used to assess fibrosis; however, alternative methods for quantifying PR staining have been shown in other tissues to allow greater sensitivity and more detailed characterization.

**Methods:** \( Pkd1^{+/+} \) mice were compared to \( Pkd1^{−/−} \) (WT). TKV was quantified from US and MRI (77 and 16T) at 1, 3, and 4 months old. US measurements of kidney and heart were made using the robotic Vevo770 system. Inter-observer variation (2 observers) was greater for US than MR, but able to detect differences between genotypes and time points. US allowed scanning in 2-5 minutes/mouse while MR required 20-30 minutes. Cylindrical light showed a greater percentage of the thickest collagen fibers in RC/RC mice, and a corresponding lower percentage of each of 3 categories of thinner collagen fibers. Preliminary data using fluorescence microscopy also showed a higher density of collagen fibers in RC/RC mice vs. WT. Analysis of collagen fiber angle, length, straightness, and width is ongoing. RC/RC had a lower GFR, higher BUN, and elevated cAMP vs WT. No differences were observed in cardiac function (ejection fraction, heart rate, or cardiac output).

**Conclusions:** These studies demonstrate the utility of US and alternative approaches of quantifying fibrosing using PR.

**Funding:** NIDDK Support

**PO1269**

Phenotypic Heterogeneity in Type IV Collagen-Associated Nephropathy: The Cystic Phenotype

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**Background:** Exome sequencing (ES) revealed mutations (mut) in type IV collagen (COL4) genes in patients (pt) diagnosed with other forms of chronic kidney disease (CKD), supporting the concept of spectrum of phenotypes for COL4-Nephropathy. Unexpectedly, some pt with CKD presenting with cystic phenotype were identified with COL4-Nephropathy by ES.

**Materials and Methods:** The retrospective study included 130 pt referred to outpatient clinic of genetic kidney diseases of ASST Spedali Civili di Brescia from 2002 to 2021 and diagnosed with COL4-Nephropathy. Based on the presence of multiple and bilateral renal cysts on imaging (fig1), a group of pt with cystic phenotype was selected (27/130,21%).

**Results:** Among cystic group (CG), diagnosis was based on genetic test (g) and kidney biopsy in 10/27 pt, whereas it was "biopsy-proven only" in 7 pt, gt-based in 3 pt and clinically in 7 pt. Fifteen pt underwent gt (fig2): heterozygous mut in COL4A3 and COL4A4 were detected in 9 and 3 cases, respectively; 1 patient showed mut in COL4A5 and 2 pt had a digenic pattern. At baseline, comparison between CG and non-CG showed lower eGFR (70[IQ 35;91] vs 91[IQ 74;114] mL/min/1.73m\(^2\)) and proteinuria (1.1 vs 0.38 g/24 hrs), although the statistical significance was not reached for proteinuria (p=0.058). At last censoring, data confirmed a lower eGFR (26[IQ 7;55] vs 86[IQ 44;143]) and a tendency (p=0.045) of greater arteriolar thickening in CG. Prevalence of arterial hypertension, CKD (defined as eGFR < 60) and ESKD was higher in CG.

**Conclusions:** The study contributes to expand the emerging phenotypic heterogeneity of COL4-Nephropathy and suggests that cystic phenotype could predict progression of kidney disease.
POI1270

Rare Variants in Syndromic Ciliopathy Genes as Novel Causes of Isolated Renal Disease in Adults

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Background: Renal ciliopathies are among the commonest genetic causes of end-stage renal disease (ESRD). Ciliopathies are caused by defects of the primary cilium, an antenna-like organelle with mechanochemical roles, crucial for organ development and maintenance. Disorders of the cilium present early with multi-organ involvement, but some individuals present as adults with organ-specific phenotypes, potentially due to milder mutations and organ-specific effects.

Methods: We identified rare variants in two ciliopathy genes in two unrelated adults presenting with ESRD. ACMG guidelines did not classify these variants as pathogenic, requiring functional validation to establish a causal genotype-phenotype relationship.

Results: Bi-allelic CC2D3 missense variants were identified in a patient, with ESRD, suggestive of an isolated renal ciliopathy. CC2D3 is essential for ciliogenesis, with complete loss of cilia in knockout mice (Development 135:4049 2008). Severe mutations were reported in patients with a syndromic ciliopathy (OPD X; OMIM# 615948), but no cases of isolated renal disease have been reported. We detected a moderate but consistent shortened cilia length in skin fibroblasts and renal epithelial cells from our proband, suggestive of a milder ciliary defect. Remarkably, the proportion of ciliated cells was significantly reduced in renal epithelial cells but not in fibroblasts, cells from our proband, suggesting a milder ciliary defect. Pathogenic variants in CC2D2A cause Joubert and Meckel syndrome, with no isolated renal presentations observed to date (Mol. Genet. Genom. e1603 2021). We identified a novel homozygous nonsense variant (Arg34*) in CC2D2A, classified as not pathogenic due to an alternate start-codon, in a previously healthy 37-year-old male with isolated ESRD of unknown etiology. Using public data (GTEx), we show that protein-coding transcripts harbouring this variant are the predominant transcripts in the kidney when compared to tissues relevant to CC2D2A-related phenotypes (e.g., cerebellum, liver).

Conclusions: Rare variants in known syndromic ciliopathy genes cause isolated renal disease in adults due to potential organ-specific effects. Using variant classification schemes without functional analysis may not accurately capture the genetic contribution to adult ESRD.

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POI1271

Targeted Exome Sequencing Application for Genetic Diagnosis of Pediatric Patients with Cystic Kidney Disease

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Background: Detection of a mono- genetic cause of chronic kidney disease accounts for almost 30% of cases in the pediatric cohort. Of these, the highest yield in the genetic diagnosis is currently seen in cystic kidney disease. Nearly 100 monogenic causes of renal cystic ciliopathies have been identified and the genetic diagnostic yield is reported to be approximately 50%. Here, we report the results of genetic testing in a cohort of Korean pediatric patients with cystic kidney disease.

Methods: From July 2019 to February 2021, children under the age of 18 with three or more cysts in both kidneys on imaging studies were recruited from three nephrology centers in Korea. Genetic identification was performed by targeted exome sequencing (TES) including 89 genes known as cystogenesis-related or causative-ciliopathy.

Results: A total of 46 pediatric patients with cystic kidney disease were recruited. The median age was 9.2 years (IQR, 5.49-14.53) and 60.9% were boys. Twelve patients (27.9%) had a family history of cystic kidney disease. The clinical diagnoses of the patients were 10 patients with autosomal dominant polycystic kidney disease, 5 patients with autosomal recessive polycystic kidney disease, 2 patients with multicystic dysplastic kidney, 1 patient with nephronophthisis, and the others were undiagnosed. The mutation detection rate was 52.2% (24 of 46). PKD1 was the most common causative gene (16 patients, 34.8%), followed by HNF1B (3 patients), PAZ2 (2 patients), PKD2 (1 patient), PKHD1 (1 patient) and NPHP3 (1 patient). Genetic mutations were identified in all patients (12 of 12) with a family history of cystic kidney disease. In patients without a family history, genetic mutations were found in 35.3 % (12 of 34).

Conclusions: The mutation detection rate in this cohort of Korean pediatric patients with cystic kidney disease was 52.2% by TES. Mutations in PKD1 were found most commonly, and the mutation detection rate was higher in patients with a family history of cystic kidney disease. For children with cystic kidney disease, molecular genetic testing is essential for an accurate diagnosis, personalized treatment, and prognosis prediction.

Funding: NIDDK Support

POI1272

The Prognostic Factors of Cyst Infection due to ADPKD

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Background: Renal or hepatic cyst infection is a complication of autosomal dominant polycystic kidney disease (ADPKD), which requires hospitalization and causes death. Cyst aspiration was the gold standard to diagnose this disease. Because of its invasiveness, several diagnostic criteria without using cyst aspiration have been proposed, but prognostic factors of cyst infection have not been analyzed in this setting.

Methods: Inclusion criteria of this retrospective cohort are ADPKD patients who were admitted in Toranomon hospital and Toranomon hospital Kaiyoga between 2016 April and 2021 March, and who were diagnosed as cyst infection based on MRI findings, which we previously published. Primary composite endpoint was defined combination of death, septic shock, or hospitalization for more than four weeks, and secondary outcomes were defined by each outcome mentioned above. Logistic analysis was planned to assess the predictors of the outcomes.

Results: One hundred ninety patients were eligible to this study. The average age was 65.0±9.2 years, 116 (61.1%) were female, and the average height-adjusted total liver volume (htTLV) was 332±2286 mL per meter, and 164 (86.3%) had hemorrhoidal therapy. Composite outcome occurred in 109 (57.4%): 25 death, 36 shock, and 98 longer-hospital-stay. Multivariable logistic regression model after adjusted related variables showed that older age (odds ratio(OR) 1.10 (95% confidence interval: 1.10-2.54), p-value=0.02), male (OR 2.49(1.16-5.33), p-value=0.02), higher htTLV (OR 2.29(1.39-3.77), p<0.01), lower mean blood pressure at admission (OR 0.735(0.579-0.9319), p<0.01), larger size of infectious cyst (OR 1.42(1.06-1.91), p<0.02) were significantly associated with the composite outcome. Although the culture-positive case or higher white blood cell count were not significantly associated with the primary outcome, they were associated with septic shock due to cyst infection.

Conclusions: Baseline characteristics at admission were associated with the prognosis of cyst infection diagnosed by MRI-based criteria, which was similar to cyst infection diagnosed by cyst aspiration. Culture-positive case or higher white cell count were reported as risk factors requiring more invasive therapies that could lead to septic shock and need longer hospitalization in our study’s cohort.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

409
PO1273
ExoGAG, A New Method for Extracellular Vesicle and Glycoprotein Isolation in Urine That Unmasks the Pathophysiology of the Kidney and Identifies New Biomarkers of Kidney Disease

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Background: Glycosaminoglycans (GAGs) are large polysaccharides that interact through glycosidic bonds with proteins and lipids, forming the extracellular matrix; or with secreted proteins, as uromodulin. Glycosylation is altered in pathologies, as cancer or kidney diseases. GAGs are present in extracellular vesicles (EVs), nanometric structures delimited by lipid bilayer that cells release and whose charge (RNA/miRNA, DNA and proteins) is essential in intercellular communication. Our group developed a method for GAG, glycoproteins and EVs isolation in any biological sample, called ExoGAG (commercialized by Nasas Biotech), which led us to identify and characterize new signalling mechanisms, and identify new prognostic/diagnostic biomarkers, for example, in polycystic kidney disease (PKD).

Methods: Urine samples have been collected from patients genetically diagnosed with type I and II PKD at different stages of disease. Using ExoGAG, GAG-glycoprotein-EVs complex has been isolated and characterized by different proteomic techniques (Western Blot, mass spectrometry), gene expression (RT-PCR), and image characterization (electron microscopy, immunofluorescence).

Results: ExoGAG has allowed us to identify a new biomarkers in urine (in protection) in PKD patients, which are altered in disease progression, even anticipating currently used kidney markers. The characterization of these complexes has led us to discover signalling mechanisms between the different segments of the nephrons, and whose function is altered in different pathologies. These findings have served other researchers deepen knowledge in different specialties such as Oncology and Endocrinology.

Conclusions: This new method for isolating the fraction associated with GAG in urine samples has allowed us to identify prognostic/diagnostic biomarkers of kidney diseases, based on glycoprotein and vesicular profile. Likewise, it has led us to identify new signalling mechanisms of the nephron, which opens a new field for a better understanding of renal pathophysiology. These results uncovered the potential to identify new signalling mechanisms between the different segments of the nephron, and whose function is altered in different pathologies. These findings have served other researchers deepen knowledge in different specialties such as Oncology and Endocrinology.

PO1274
Deposition of an Abnormal Extracellular Matrix as an Initiating Event in Cyst Formation

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Background: Extracellular matrix (ECM) refers to the proteins and other macromolecules outside of cells that provide a scaffolding to maintain tissue architecture. The distinct ECMs to which these cells are attached, epithelial cells to a laminin-rich basement membrane vs. interstitial cells to a collagen/fibronectin (FN) ECM, has profound implications for cell behavior and tissue architecture. These differences in cell behavior are mediated through a family of receptors known as integrins, used by cells to attach to the ECM. Here we provide evidence that cyst formation in ADPKD is a manifestation of abnormal cell behavior in response to an atypical extracellular matrix and changes in integrins.

Methods: To understand the pathological contribution of integrins and FN to ADPKD, we measured their expression and localization in vivo using a postnatal murine model of ADPKD and kidney samples from human ADPKD.

Results: We observed increased expression of FN in murine cystic kidneys and also in kidneys from humans with ADPKD. In mice, increased fibronectin expression preceded cyst formation. Moreover, laminin basement membrane underlying cyst lining cells was discontinuous and replaced in some sections by a FN-rich ECM. Some sections were conspicuous for expressing the FN receptor α5β1 integrin, and for cell morphology being cuboidal instead of flattened. In other areas of the FN rich ECM, αv-integrins, were present on flattened cyst lining cells. αvβ1 integrin was more abundant on cyst lining cells than on non-cystic tubules. Interestingly, in situ hybridization revealed that Fn1 was not expressed in all cyst lining cells but in the specific subset of cells that had a cuboidal appearance.

Conclusions: Our studies presented here identify a distinct subset of cuboidal cyst lining cells that express Fn1. They also demonstrate distinct integrin repertoires among subtypes of cyst lining cells. As FN deposition precedes cyst formation, these FN-expressing cuboidal cells may have a role in the initiation or early progression of cysts in ADPKD.

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410

PO1275
Uncovering the Role of the Extracellular Matrix in ADPKD Progression

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Background: Polycystic Kidney Disease (PKD) is a genetic disorder due to mutation in either Pkd1 or Pkd2 genes and characterized by bilateral cysts formation. We recently uncovered a direct role of Pk1, the protein product of Pkd1 gene as a mechanosensor of extracellular stiffness. We found that Pk1-1 interactors mediate inhibition of actomyosin contraction that mediates the cellular response to the rigidity of the Extracellular Matrix (ECM). Based on these findings we speculated that Pkd1 cells fail to properly respond to the extracellular mechanical force of ECM leading to excessive matrix deposition and proliferation. In line with this, kidneys of end-stage PKD patients show enhanced fibrosis typical of cystic kidney disease and tumors. We then wondered whether PKD ECM is a part of an active Cyst Microenvironment (CME), exerting a key role in the evolution of the disease.

Methods: We characterized CME in the renal tissue of an aggressive Pkd1-/-/Cre- and a low progressive Pkd1-/-/Tam-Cre inducible mouse models. To study the composition and the mechanical properties of the cystic ECM we decellularized cystic kidneys obtaining ECM-derived kidney scaffolds. Furthermore, we isolated matrix from Pkd1 fibroblasts in vitro.

Results: We have characterized the renal tissue microenvironment of two Pkd1 inducible mouse models at a late stage of the disease confirming the presence of fibrosis, immune infiltrates and progressive accumulation of collagen I. In line with an active role for ECM in the progression of disease, we found that fibroblasts in the deposition and remodeling of the ECM, our data showed the presence of activated fibroblasts in cystic kidneys. We performed a proteomic analysis of cystic kidney scaffolds by Mass Spectrometry (MS). Cluster analysis of MS data showed a clear separation between cystic and control scaffolds. Finally we found that matrix isolated from Pkd1-/- cells was able to influence differently key cellular properties such as adhesion, polarization, proliferation and migration.

Conclusions: ECM plays an active role in the progression of ADPKD disease.

PO1276
Abstract Withdrawn

PO1277
17q12 Deletion Syndrome Presenting as Congenital Diaphragmatic Hernia in a 2-Month-Old Infant


Introduction: 17q12 deletion syndrome results from the loss of as many as 15 genes on the long arm of chromosome 17 including the hepatocyte nuclear factor-I-gamma (HNF1B). Heterozygous pathogenic variants, whole gene deletion, or duplication in HNF1B are frequently linked to inherited kidney malformations including hyperechogenic kidneys, kidney cysts, solitary kidney, and hydrenephrosis as well as extrarenal phenotypic features. 17q12 deletion syndrome has also been linked to congenital diaphragmatic hernia (CDH). We present a case of an infant with hyperechogenic and cystic kidneys, diagnosed postnatally with CDH.

Case Description: A 2-month-old female with a history of hyperechogenic kidneys on prenatal ultrasound presented to the emergency department with increased work of breathing. A chest x-ray revealed left hemidiaphragm elevation, normal cardiac silhouette, and no focal pulmonary consolidation. Computed tomography of the chest confirmed the diagnosis of CDH. A repeat kidney ultrasound revealed diffuse hyperechogenic kidneys and a focal kidney cyst within the right upper pole (Image 1). Genetic workup revealed a 1.9 megabase deletion on the long arm of chromosome 17 consistent with the diagnosis of 17q12 deletion syndrome.

Discussion: Pathogenic variants in HNF1B or whole gene deletion as part of 17q12 deletion syndrome should be considered in infants with hyperechogenic kidneys with cysts, particularly in the context of extrarenal manifestations. Studies have examined the link between HNF1B and the development of a CDH. It is proposed that HNF1B is involved in the WNT signaling pathway that is critical to mesodermal differentiation and proper diaphragm formation. Only 4 other cases of HNF1B mutations associated with CDH are reported in the literature. Two cases describe HNF1B deletions, and 2 cases describe HNF1B duplications. It is possible that the high prenatal mortality of CDH could explain the paucity of this association.
POI1278

Recurrent Pneumothorax in a Marfanoid Adolescent with Autosomal Dominant Polycystic Kidney Disease

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Introduction: Pneumothorax may be a rare extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD), and may indicate co-inheritance of other genetic diseases.

Case Description: A 21-year-old man with ADPKD and pneumothoraces presented to nephrology clinic. A screening ultrasound in late childhood was completed due to his family history and confirmed ADPKD. The patient was normotensive and had a tall, thin habitus. His musculoskeletal examination was pertinent for several marfanoid findings, including increased arm span ratios, pes planus, and positive thumb and wrist signs. His eGFR was normal and he did not have proteinuria. He was hospitalized several times between ages 13-20 for recurrent pneumothoraces requiring left apical wedge and lower bleb resections with pleurectomy, and right upper lobectomy and pleurectomy.

Discussion: The patient’s lung collapse was attributed to primary spontaneous pneumothorax due to his tall stature and intermittent tobacco use. However, this cannot account for his high rate of recurrence. The extent of pneumothorax burden in this patient should be considered in context of his underlying polycystic renal disease. Pulmonary manifestations of ADPKD are not well understood and have only been described in a handful of case reports. Bronchiectasis and cystic lung disease are thought to occur as a downstream consequence of impaired parenchymal healing. Mutated polycystin-1 in ADPKD prevents normal ciliary function, which is imperative for coordination of cellular repair in bronchial smooth muscle cells. Evolving cystic lung disease in the setting of underlying ADPKD could explain this patient’s recurrent pneumothoraces. The possibility of a co-inherited connective tissue disease should also be considered in patients with ADPKD and pneumothoraces. "Overlap" disorders between ADPKD, Marfan syndrome and Tuberous Sclerosis (TSC) have been examined in linkage studies, and have chromosomal proximity. Marfan syndrome and TSC are associated with pneumothorax. Though our patient did not manifest criteria for TSC, his examination is consistent with a Marfan’s variant phenotype. This patient may be an example of co-inherited disease, and raises the question of whether it is under this circumstance that rare pulmonary complications become apparent. Clinicians should be aware of these overlap disorders in relation to ADPKD.

POI1279

Ruptured Intracranial Aneurysm as the Initial Presentation of ADPKD in a Pediatric Patient

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is associated with multiple extra-renal manifestations, most notably intracranial aneurysms (ICA). Approximately 10% of ADPKD patients develop ICA during their lifetime. Subarachnoid hemorrhage (SAH) is a major complication of ICA and usually occurs during the end of the 3rd decade. Aneurysm rupture in children <18 years of age is extremely rare. We report a case of a 9-year-old boy presenting with symptomatic ICA rupture as the initial presentation of ADPKD, despite a negative family history of ICA.

Case Description: A 9-year-old boy presented to the emergency department with an abrupt onset of severe headache and lethargy after a fall. His family history was remarkable for ADPKD in his father and grandfather. None of his affected family members developed ICA or intracranial hemorrhage. Initial non-contrast computed tomography scan of the head showed frontal lobe hemorrhage. Additional imaging studies revealed a ruptured anterior communicating artery with SAH. Urgent aneurysm coiling was performed, his bleeding was controlled, and the patient survived. Due to his strong family history for ADPKD, a kidney ultrasound was performed and showed enlarged kidneys with multiple renal cysts bilaterally confirming the diagnosis of ADPKD. The patient’s father underwent a screening MRI of the brain at the age of 48 years and was negative for ICA.

Discussion: Our case of SAH due to ICA rupture as the initial presentation of ADPKD, in the absence of a positive family history of ICA or hemorrhage, has not been reported in children. Rare cases of subarachnoid hemorrhage in pediatric patients with ADPKD and a positive family history of ICA or hemorrhage have been described. Based upon available data, it is unclear if either widespread or targeted screening for intracranial aneurysms is beneficial for pediatric patients with ADPKD. Screening is reserved for patients with a family history of hemorrhage, migraine, stroke, patients undergoing major surgery, or patients with high-risk jobs. However, we do not screen children <18 years of age because of the extreme rarity of aneurysmal rupture at that age. Though extremely rare, radiologists, care physicians and pediatricians should stay aware that ICA rupture occurs in children with ADPKD and may lead to devastating complications, even in the absence of positive family history.

POI1280

Congenital Solitary Kidney in ADPKD: A Genotype-Phenotype Correlation

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Introduction: There are a very few cases of ADPKD associated with Unilateral Renal Agenesis (URA). The total amount is currently 9 cases known in the world and their renal function outcome is somewhat undefined.

Case Description: ZG is a pleasant 41-year-old man with a congenital solitary left kidney with multiple cysts and a genetic diagnosis of ADPKD. Familiarity is negative for ADPKD, but positive for URA (present in his sister and her son). Except for hypertension, there are no extrarenal ADPKD manifestations. Poster et al. analyzed 3 patients with a similar phenotype in a cohort of 182 ADPKD subjects, comparing how the volume of the single kidney increased (SKV) over time and how the GFR dropped, stratifying them for sex and age. A greater SKV in time has been recorded in these 3 patients, caused by both compensatory hypertrophy and cyst growth. Surprisingly though, their kidney function was better compared to controls. Late onset kidney failure is probably caused by hyperfiltration, and it is linked with a long-term worse outcome. In our case, ZG’s SKV increased less compared to another subject with same age and sex and with controls found in literature. Same goes for kidney function, which was better and more stable in a 10-year time-lapse compared to controls.

Discussion: The reason for this could be found in the PKD1 mutation: ZG has a missense mutation, while the aforementioned 3 cases had truncating ones. ZG’s increased SKV is probably more related to hypertrophy than cyst growth itself. Therefore, even in an unorthodox situation like this one, long-term outcome seems to depend on the genotype of the subject.

Note: Table shows values of SKV for patient ZG and patient with polycystic solitary kidney. For the matched 2-kidney ADPKD group is reported the SKV mean values with 95% CI. For this last group the volume given is that of the left kidney present in the other 2 cases. SKV is calculated from RMN scans. Creatinine clearance is estimated according to the Cockcroft-Gault formula. In the 2-kidney ADPKD group CCR is estimated by calculating both kidneys.

POI1281

Management of a Patient with ADPKD Who Needs Lithium

Katharine L Senter, Omar H. Maarouf, JingJing Zhang. Thomas Jefferson University Sidney Kimmel Medical College, Philadelphia, PA.

Introduction: N/A

Case Description: A 35-year-old female with borderline personality disorder and schizoaffective disorder presented to nephrology for autosomal dominant polycystic kidney disease (ADPKD). Her biological father had ADPKD and was on dialysis at the time of death. The patient has taken lithium for 10 years, and only lithium allows her to work and live independently. She presented with polydipsia and polyuria, indicating possible nephrogenic diabetes insipidus (DID) from lithium, essential hypertension since age 30, and constant headache; brain MRI was negative for aneurysm. Labs showed a lithium level between 0.3-0.9 mmol/L, creatinine between 0.6-0.75 mg/dL, GFR of 85-90 ml/min, urine protein/creatinine ratio of 0.27-0.32 g/g, and urine osmolality <100 mOsmol/kg.

She was treated with 2.5 mg lisinopril, 10 mg amiloride, and 1350 mg lithium daily. Abdominal MRI without contrast showed scattered liver cysts and innumerable bilateral kidney cysts. Kidney volume indicated Mayo Class 1C PKD. Her father developed ESRD in his late 50s, suggesting rapidly progressive ADPKD class. Lithium nephropathy is usually characterized by 1-2 mm renal microcysts (Khan et al., Int J Psychiatr Med 50(3):290-298). The patient’s larger cysts, total kidney volume, and liver cysts suggest ADPKD. Genetic testing showed that the patient has a heterozygous mutation in c.12445+1G>T, expected to cause altered splicing and function of the PKD1 gene.
Discussion: Finding an appropriate agent to slow CKD progression is the current strategy to manage PKD. Her condition is complicated by likely lithium nephropathy. The TEMPO trial (Torres et al, N Engl J Med 367:2407–2418, 2012) showed that tolvaptan helps slow rapidly progressive ADPKD by inhibiting vasopressin’s effect, reducing cAMP production, further inhibiting cyst formation and growth (Wang X et al, J Am Soc Nephrol 19: 102–108, 2008; Aihara M et al, J Pharmacol Exp Ther 349: 258–267, 2014). Lithium can also inhibit vasopressin in the kidney, leading to nephrogenic DI (Bokenhauer et al, Nat Rev Nephrol11(10):576-88, 2015). In ADPKD, tolvaptan helps achieve a urine osmolality of less than 300 mOsmol/kg (Torres, Clin J Am Soc Nephrol. 13(11):1765-1776, 2018). Our patient already has polycystia and urine osmolality below 100 mOsmol/kg. Her condition requires agents targeting other pathways. For now, she is on lisinopril, with BP <110/75, and amiloride to limit polyuria.

PO1282
A Case of Mistaken Identity: Alport Syndrome Masquerading as Polycystic Kidney Disease
Kana R. Amari, Jennifer A. Tuazon. Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: Alport Syndrome (AS) is an inherited nephritis caused by a collagen-IV-related mutation leading to abnormalities in the glomerular basement membrane. Patients may present with unexplained hematuria, proteinuria, with or without renal insufficiency. Here, we describe two cases of patients presenting with multiple bilateral renal cysts, initially diagnosed with autosomal dominant polycystic kidney disease (ADPKD), who were later found to have Alport syndrome via genetic testing.

Case Description: We report two cases of patients followed in our nephrology clinic who were initially thought to have ADPKD. The first patient is a 75-year-old woman who was followed for long-standing hematuria, CKD3aA2, sensorineural hearing loss, retinal detachment, and a family history of cystic kidney disease. Due to normal kidney sizes, genetic testing was done which revealed a pathogenic COL4A3 mutation, c.1372G>C (p.Gly458Arg). Our second patient is a 64-year-old man with a history of hematuria, CKD3aA2, bilateral renal cysts, initially diagnosed with autosomal dominant polycystic kidney disease. The first patient is a 75-year-old woman who was initially thought to have ADPKD. The second patient is a 64-year-old man with a history of hematuria, proteinuria, with or without renal insufficiency. Here, we describe two cases of patients presenting with multiple bilateral renal cysts, initially diagnosed with autosomal dominant polycystic kidney disease (ADPKD), who were later found to have Alport syndrome via genetic testing.

Discussion: Very few cases have described an association with AS and cystic kidney disease. The causal mechanism for renal cyst formation and Alport syndrome is unknown. These cases illustrate the importance of considering alternate diagnosis when suspected ADPKD has atypical features such as normal kidney sizes or kidney dysfunction more than expected for the cyst burden.

PO1283
Heterozygous HSD11B2 Gene Mutations and Apparent Mineralocorticoid Excess (AME) in a Patient with Heterozygous ADPKD1
Celeste S. Chang,1,2 Hsiang C. Liu,1 Chinatown Kidney Care, New York, NY; Mount Sinai Beth Israel Hospital, New York, NY; Wei Gong Memorial Hospital, Taofen, Taiwan.

Introduction: HSD11B2 gene which locates at Chromosome 16q22.1 and encodes the Type 2 isoform of 11-beta-Hydroxysteroid Dehydrogenase that interconverts biologically active cortisol and inactive cortisone. Polycystin-1, encoded by the PKD1 gene, which locates at Chromosome 16p13.3. PKD1 gene forms a complex with polycystin-2 (PKD2) that regulates multiple signaling pathways to maintain normal renal tubular structure and function. We present a new finding of HSD11B2 gene in a patient with polycystic kidney disease.

Case Description: 58-year-old Chinese male presented with bilateral renal cysts and CKD Stage 3 A. PMHx is significant for early onset HTN at the age of 45, Left ICH without residual weakness at the age of 46 years and episode of hypokalemia. Denied Licorice ingestion. Family history is positive for HTN and polycystic kidney disease in his mother and all three siblings. His BP was 145/91 mmHg, not controlled well with daily dose of oral Lisinopril 40 mg and Amlodipine 10 mg. His Na 141, K 4.7, CO2 27, BUN 20, Cr: 1.6, GFR: 46, Hb 12.5 and Urine protein/ Cr ratio was 0.324. He was started with low dose of Spironolactone 12.5 mg daily for BP control and proteinuria. Renal ultrasound showed Right kidney was 19.5 cm, left kidney was 18.6 cm and presence of multiple bilateral renal cysts. Abdominal CT without contrast disclosed H1TKV: 1724 ml/m. Mayo clinic class was 1 C; estimated frequency of ESRD at 10 years was 37.8%. Kidney gene panels detected the gene of PKD1 (Autosomal Dominant) and HSD11B2 (Autosomal Recessive). BP stable at 125/78 mmHg, 24-hour urine protein was 125 mg per day, Serum cortisol 11 mcg/dl (normal: 8-19 mcg/dl), Serum cortisone: 0.74 mcg/dl (normal: 1.34-2.65 mcg/dl), Serum cortisol/cortisone ratio: 17.6 (normal: 3.3-9.1), 24 hours Urine free cortisol: 7 mcg/day (normal 5-64 mcg/day), 24 hours Urine free cortisone: 31 mcg/day (normal 16-128 mcg/day), 24 hours Urine free cortisol/cortisone ratio: 0.22 after spironolactone. However, it was discontinued upon repeated serum K was at the higher side of normal. He is currently treated with oral Tolvaptan. 

Discussion: This is an unique case which could be the first case report of HSD11B2 mutations with apparent mineralocorticoid excess associated with heterozygous ADPKD1.

PO1284
A Rare Presentation of Autosomal Recessive Polycystic Kidney Disease in Adulthood
Katerina Hysi, Saira Sajid, James Drakakis. NYU Winthrop Hospital, Mineola, NY.

Introduction: Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatoportal fibrocystic syndromes and causes significant renal and liver related morbidity and mortality in children. Renal cysts, congenital hepatic fibrosis, and recessive inheritance characterize ARPKD. The disorder usually manifests infancy, with a high mortality rate in the first year of life. For the patient who survives the neonatal period, the probability of being alive at age 15 ranges from 50-80%, with the majority requiring renal replacement therapy at that age. This diagnosis is rarely made in the adult years with the clinical course and prognosis much less well defined.
Case Description: 57-year-old male with PMHx of gout and long standing CKD with creatinine 1.9 mg/dl, daily back pain, bilaterally. His urine was sent to MOI in 2010 with little progression presented for evaluation. Urinalysis was without microscopic hematuria or proteinuria. Historic imaging showed small kidneys and medical renal disease. An updated MRA noted bilateral kidneys cysts with areas of atrophy and scarring, which along with an increase in his liver transaminases raised suspicion for ARPKD. The patient subsequently underwent whole exome sequencing, which confirmed two pathogenic variants (specifically S3018F and R1624W) in the PKHD1 gene, consistent with ARPKD. His brother was eventually tested as well and found to have the same two variants.

Discussion: The classic presentation for ARPKD is systemic hypertension with progression to ESRD by the age of 15. In a typical presentation, a small number of those with ARPKD live to adulthood with some compromise of kidney function; but with significant variability. ARPKD is a lethal disease. Due to its wide phenotypic variability, the diagnosis of ARPKD may be made during any stage of childhood; in rare cases, it does not present until adolescence or adulthood. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction or otherwise unexplained renal cysts as the prominent presenting feature. This case exhibits the silent menace of ARPKD with a delay in recognition of clinical manifestations and thus an unusually older age at the time of diagnosis.

**PO1285**

HDR: A Novel Mutation in GATA-3 with Variable Expressivity in an Affected Family

Meneukshi Sambaria, Jason Misurac, Christie P. Thomas. The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA.

Introduction: Hypophosphatemic rickets, a disorder also known as Barakat syndrome, is a rare autosomal dominant disorder caused by a mutation in the GATA3 gene. Hypophosphatemic rickets is a multisystemic disease with manifestations involving bone, teeth, muscle, kidney, eye, and skin. The majority of affected patients have renal osteodystrophy, with or without sensorineural hearing loss. The missense variant described in our patient has not been previously reported, although an

Underline represents presenting author.

**PO1286**

Assessing Genomic Needs

Jordan G. Nestor,1 Sumit Mohan,1 Ali G. Gharavi,1 Chunhua Weng,1 Jun C. Suh,1 Columbia University, New York, NY; 2Columbia University Mailman School of Public Health, New York, NY.

Background: Interventions must address nephrologists’ knowledge gaps, perceived needs and preferences for genomic data to guide personalized patient care. Previous studies have identified gaps in nephrologists’ knowledge of genomics and can inform the design of tailored interventions that address nephrologists’ needs, including education, workflow and clinical-decision support tools. Together, such tools can promote wider utilization of genomic resources and empower nephrologists to use genomic data.

Results: Between January-May 2021, 319 complete surveys were eligible for analysis by nephrologists across 47 U.S. States, (86% adult vs. 14% pediatric), with 34% community-based (vs. 66% academic) including 36% who perform transplant evaluations and 75% with prior experience ordering genetic testing; 77% responded that genetic test results have meaningful implications for a patient’s care; 91% were aware that a tailored lab report would be helpful; 53% identified important for disease diagnosis (92%), understanding (85%), prognosis (86%), treatment (88%); 86% indicated that a personalized lab report would be helpful. Most had referred > 20 patients for GT (61%). GT was considered clinically important for disease diagnosis (92%), understanding (85%), prognosis (88%), treatment planning (93%). 68% report they have reliable information for care of patient with genetic results. Top 3 challenges to GT included interpretation of results, selection of test, and ordering test. 86% felt patients could afford GT. Most indicated the importance of having clear guidelines for GT (84%). Majority (70%) would recommend GT for family members, especially in the presence of a tailored lab report (91%).

**PO1287**

Pediatric Nephrologists’ Perspectives on Genetic Testing and Return of Results to Children


Background: Pediatric (ped) nephrologists care for children with genetic causes of chronic kidney disease (CKD). While genetic testing (GT) is now more accessible in nephrology, little is known about the utility, clinical application, and relevance of GT in determining underlying CKD or other actionable secondary genetic findings for ped nephrology patients. We explored ped nephrologists’ views regarding GT in clinical and research settings.

Methods: An online 30-item survey was developed and distributed via professional listservs. Inclusion criteria required self-identification as a U.S. licensed nephrologist. Data collection was from 1/22/21-5/4/2021 and analyzed by STATA 15A. Descriptive statistics are reported.

Results: 85 ped nephrologists completed the survey. Respondents range in yrs in practice (35% 6-15 yrs, 21% 16-25 yrs, 28% > 25 yrs), and 75% practiced in a university hospital. Most had referred 20 patients for GT (61%). GT was considered clinically important for disease diagnosis (92%), understanding (85%), prognosis (88%), treatment (93%). 68% reported they have reliable information for care of patient with genetic results. Top 3 challenges to GT included interpretation of results, selection of test, and ordering test. 86% identified fitting GT into practice as a challenge, and 61% report offering counseling with a genetic expert after return of genetic results. 53% felt patients could not afford GT. Most indicated the importance of having clear guidelines for GT (84%). Majority (70%) would recommend GT for family members, especially in the presence of a tailored lab report (91%).
are involved in the return of results in their own practice (60%). Regarding the return of research-based results, most thought diagnostic (92%) and actionable secondary findings (75%) should be returned.

Conclusions: Ped nephrologists report on the importance of GT in CKD. They also report on their personal challenges with GT and structural barriers to the utilization of GT.

Funding: NIDDK Support

POI1288
Attitudes and Perceptions of APOL1 Genetic Testing in Black Patients with Hypertension: A Pilot Study
Krista L. Lentini,1 Anthony N. Muiru,2 Kathryn K. Lindsay,1 Amy Mosman,1 Yasar Caliskan,3 Barry J. Friedman,1 Amber Carrick,4 Chi-yanu Hsu,1 Kana N. Miyata,1 Thanh-Mai N. Vo,1 John C. Edwards,2 Marie D. Philipneri,3 Saint Louis University School of Medicine, Saint Louis, MO; 2University of Washington, Seattle, WA; 3Wake Forest University School of Medicine, Winston-Salem, NC; 4Mid-America Transplant Services, Saint Louis, MO.

Background: A portion of the chronic kidney disease risk in Black persons appears due to polymorphisms in the gene encoding apolipoprotein L1 (APOL1). While applications of APOL1 genotype testing for prognostication (e.g. in evaluation of organ donors) are emerging, the interest of Black patients in APOL1 genotyping and implications for individual kidney risk management are not well defined.

Methods: In this pilot study, we offered APOL1 genetic testing and assessed attitudes and concerns related to APOL1 testing and kidney risk management among Black persons seen in the Hypertension & Nephrology clinics at one urban, Midwestern center.

Results: Among 110 participants with genotyping results to date, 56% were women, mean age was 58 years, 72% were obese, and a mean of 3 antihypertensive agents were used (Table). 13% had 2 APOL1 renal risk variants (high-risk genotypes), and 42% had 1 risk variant. At baseline, most participants (86%) reported that they were concerned about kidney disease, 90% thought it was a good idea to be tested for genes that may impact kidney disease, 82% would want APOL1 testing for their children, and only 26% expected to feel upset if they were APOL1 high risk. Most participants reported that knowledge of a high-risk APOL1 genotype would lead to changes in health-related behaviors (Figure).

Conclusions: Black patients at a Midwestern medical center were receptive towards APOL1 genetic testing and believed that testing would motivate changes in health-related behaviors. Ongoing research is needed to determine optimal patient-centered use of this emerging risk assessment tool.

Funding: Private Foundation Support

Table: Baseline characteristics of study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=118)</th>
<th>Low-risk APOL1 (n=95)</th>
<th>High-risk APOL1 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>56%</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>Age, mean, years</td>
<td>58 (12)</td>
<td>58 (12)</td>
<td>58 (14)</td>
</tr>
<tr>
<td>High school graduates, %</td>
<td>76%</td>
<td>78%</td>
<td>67%</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Elevation (m), mean</td>
<td>1,105</td>
<td>1,105</td>
<td>1,105</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Albuminuria, mg/dL</td>
<td>24.0 (24)</td>
<td>24.0 (24)</td>
<td>24.0 (24)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min*1.73m2</td>
<td>89 (106-161)</td>
<td>93 (108-156)</td>
<td>95 (7-315)</td>
</tr>
</tbody>
</table>

(1) Cohort characteristics and (2) Anticipated Behaviors if Testing showed APOL1 High-Risk Genotype

POI1289
Utility of Genetic Testing in Informing Management of Patients with Kidney Disease
Daniel W. Ross,1 Kenar D. Jhaveri,1 Laurel Kartchner,1 Dinah Clark,2 Kerry Gaj,2 Deepa A. Malieckal,1 1Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY; 2Natera, Inc., San Carlos, CA.

Background: Early identification of monogenic causes of CKD through genetic testing can improve disease treatment, inform management and improve outcomes. Genetic testing can also be useful for families with a history of CKD to plan for the future, including appropriate identification of organ donors. Here we describe the use of genetic testing, with RenasightTM, an NGS-based >380 gene panel for kidney disease, to inform treatment for patients being treated for kidney abnormalities.

Methods: We performed a retrospective analysis of genetic test results using RenasightTM (NGS-based>380 broad kidney gene panel) at a large academic center over an 18-month period. After signed informed consent, broad genetic testing was performed on blood or saliva samples from 31 patients. Genetic testing results were then related to alterations in the management of treatment of these patients.

Results: In this cohort, 41.9% (13/31) were female with an average age 51 years. The most common demographic groups were African American and Caucasian (6 patients [19-4%] each). Nineteen patients (61.3%) underwent Renasight testing due to a CKD diagnosis, 5 (16.1%) due to nephritis/nephritic syndrome, 3 (9.7%) due to proteinuria/nephrotic syndrome, 1 (3.2%) due to thrombotic microangiopathy, 1 (3.2%) due to phosphorus metabolism disorder, and 1 (3.2%) due to hemochromatosis. Positive results were identified in 12.9% (4/31) of the patients in the COL4A3, COL4A4, and APOL1 genes. Genetic testing results led to changes in management for 35.4% (11/31) of patients, confirmed diagnoses for 22.6% (7/31), provided additional diagnoses for 41.9% (13/31), and prompted family testing for 22.6% (7/31). For 4 patients with positive findings, test results impacted treatment management: 1 had transplant management impacted, 1 underwent biopsy to confirm Alport Syndrome, 1 had FSGS diagnosis confirmed and 1 underwent biopsy to confirm FSGS and initiated dialysis. Additionally, negative results led to alterations in management for 48.4% (15/31) of patients.

Conclusions: In this cohort at an academic practice, genetic testing informed nephrologists' management of patients in multiple capacities. Negative results can rule out genetic causes of disease, and carriers and variants of uncertain significance (VUS) can inform family planning decisions and enable testing in family members.

POI1290
Early Experience with Broad-Panel Genetic Testing in Pre- and Post-Transplant Evaluation of Patients with Kidney Failure
Rupi K. Sodhi,1 Amishi S. Desai,2 Jongwon Yoo,3 Divya J. Arwindeker,4 Katya Brossart,2 Hossein Tabriziani,1 Sanjeev Akkina,1 Loyola University Medical Center, Maywood, IL; 2Natera, Inc., San Carlos, CA.

Background: Genetic testing plays an important role in kidney transplantation (KT). Genetic assessment during the pre-KT workup enables more accurate estimation of the risk of recurrent kidney disease and informs treatment of recurrence living-related kidney donor selection. Testing with a broad genetic panel may be beneficial for patients with advanced disease. Here we describe an academic transplant center’s early experience with a >380-gene kidney disease panel using NGS, with variant confirmation via orthogonal methods.

Methods: Twenty-six pre- and post-KT patients underwent genetic testing between June 2020 and April 2021. Patients ranged in age from 28 to 67 years, with a median age of 31 years. Genetic testing results were correlated to clinical histories, including biopsy (when available), ultrasound results, presence of proteinuria and hematuria, demographic factors, family history and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on request.

Results: Positive findings were identified in 38.5% (10/26) of patients tested, in TTR, COL4A3, COL4A4, COL11A1, INF2, and PKD1. Two patients with a pathogenic variant in the TTR gene also had 2 APOL1 risk alleles (G1 and/or G2). Genetic findings confirmed clinical disease in 1 individual, identified a subcategory of clinical disease in 2 individuals, reclassified disease in 3 individuals, and established a molecular diagnosis in 4 individuals. In this cohort, 8 individuals received a KT, of which 6 had no pathogenic variant identified. Of those 6, two had biopsy proven glomerular disease that recurred after early KT, implicating a non-inherited cause of renal disease. Identification of positive pathogenic variants in 75% (3/4) of patients evaluated for a living related donor transplantation, prompted evaluation of the index donor.

Conclusions: Identification of patients awaiting KT who are at increased risk of a monogenic disease can result in a high yield via a broad-panel testing approach. The implications of a genetic diagnosis in this cohort are multifaceted, with potential to impact care and identify family members who may be at risk for kidney failure, and to enable early diagnosis and intervention.
Early Experience with Broad-Panel NGS Testing for Kidney Disease in a Community Nephrology Setting

Tarek Darwish,1 Katya Brossart,2 Hossein Tabriziani,2 "Kansas City Kidney Specialists, Overland Park, KS; 3Nätera, Inc., San Carlos, CA.

Background: Despite the increasing awareness of the value of incorporating genetic testing, its adoption in community nephrology settings is limited. Genetic testing can guide prognostication, targeted treatments, referral to specialists for extra-renal features, and identification of at-risk relatives. For individuals with kidney failure, additional testing can help assess the risk of recurrent kidney disease after transplant and evaluation of suitable living related kidney donors. Broad-panel testing can provide benefits over narrow panels based on clinical presentation.

Methods: Thirty-one patients with kidney disease completed genetic testing with the Nасenst¼±t (NGS-based >380-gene kidney disease panel) between October 2020 and April 2021. Median age of patients was 49 years (range: 28-78 years). Genetic testing results were correlated to clinical histories, demographic factors, family history (when available) and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on request.

Results: Positive findings were identified in 22.6% (7/31) of patients tested in the APOL1, PKD1, SLCO4A1, COL4A4, and PKD2 genes (Table 1). Testing resulted in an identification of a pathogenic variant in 85.7% (6/7) of patients and in changes in clinical management for 28.6% (2/7) of patients. Homozygosity or compound heterozygosity for the APOL1 high risk alleles G1 and G2 was identified in 9.7% (3/31) of patients and were found primarily in African American patients.

Conclusions: In the community nephrology setting, the utility of genetic testing as part of the diagnostic workup is multifaceted. As compared to selection of a narrow panel based on clinical features, use of a broad panel that includes reporting of the APOL1 high risk alleles has the additional benefit of identifying genetic causes of kidney disease with ambiguous or non-specific clinical findings.

Findings from Broad Panel Genetic Testing in Patients with Kidney Disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>NGS Results</th>
<th>Clinical Findings</th>
<th>ALSM3 (G1+G2+G3)</th>
<th>PKD1 (G1+G2)</th>
<th>SLCO4A1 (G1+G2)</th>
<th>COL4A4</th>
<th>COL4A5</th>
<th>POLY</th>
<th>ADPKD</th>
<th>ADPKD2</th>
<th>PKD1</th>
<th>COL4A3, 4, or 5</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOL1</td>
<td>1/7 (14%)</td>
<td>Pathogenic variant</td>
<td>7/7</td>
<td>1/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
<td>0/7</td>
</tr>
</tbody>
</table>

*Inheritance patterns: autosomal dominant (AD); autosomal recessive (AR); X-linked (XL)

The Emerging Role of Whole-Genome Investigation to Identify Undetected Nephropathies: The HIDDEN Study

Andrew J. Mallett,1 Amali Mallawarachchi,4 Zornitza Stark,6 Cas Simons,4 Catherine Quinlan,4 Ching Patel.4 The KidGen Collaborative ‘Toowoomba Hospital and Health Service, Toowoomba, QLD, Australia; 2James Cook University, Townsville, QLD, Australia; 3Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; 4Royal Prince Alfred Hospital, Camperdown, NSW, Australia; 5Murdoch Children Research Institute, Parkville, VIC, Australia; 6The Royal Children’s Hospital Melbourne, Parkville, VIC, Australia; 7Royal Brisbane and Women’s Hospital, Herston, QLD, Australia.

Background: 5% of Australian and New Zealand patients commencing kidney replacement therapy have an uncertain kidney disease aetiology. New approaches and tools are required to resolve such diagnostic odysseys. WGS is an emerging diagnostic technology whose role in this setting is unclear. We sought to determine the diagnostic yield of whole genome sequencing (WGS) in individuals with unexplained end stage kidney disease (ESKD).

Methods: Adult and paediatric patients reaching Chronic Kidney Disease Stage 5 before 51 years of age without an identified aetiology were prospectively recruited through an Australian national network of 18 clinics. Eligibility was determined by a national clinical committee based on pre-specified criteria. Clinically-accurated WGS analysis was undertaken with a curated “KidneyOme” virtual panel of genes associated with inherited kidney diseases. A genomic diagnosis constituted a KidneyOme result of pathogenic or likely pathogenic variant/s of appropriate zygoty.

Results: 168 individuals were referred (2018-2021) of whom 147 were approved and 104 consented. Of these, 40 (38.5%) were female and median age was 43yrs; 41 (39.8%) had an eGFR ≤ 90 mL/min/1.73m² and ESKD before 30yrs and 63 (60.6%) had undergone native kidney biopsy. Of 50 results returned to date, 7 (14%) were diagnostic, including both autosomal dominant (4/7) and recessive (3/7) inheritance patterns with 6/7 having a family history of CKD. A further 14/50 had variants of uncertain significance. One diagnosis was due to a copy number variation. The KidneyOme virtual panel curation of 384 genes is publicly available in PanelApp-Australia.

Conclusions: One in seven patients with ESKD of uncertain aetiology had an undetected underlying monogenic cause for their kidney disease. Application of KidneyOme with WGS has clinical utility and should be considered in younger patients with unexplained renal failure.

Funding: Government Support - Non-U.S.

The Utility of an Inherited Kidney Disease Clinic Employing a Broad Range of Genomic Testing Platforms: Experience of the Irish Kidney Gene Project

Elhussein A. Elhassan,1,3 Katherine A. Benson,2 Susan L. Murray,1 Kane E. Collins,5 Edmund H. Gilbert,1 Dervla M. Connaughton,1,5 Claire Kennedy,1 Mark A. Little,6 Gianpietro Cavalleri,2 Peter J. Conlon,1,3 sailhamer Hospital, Dublin, Ireland; 2Royal College of Surgeons in Ireland Department of Molecular and Cellular Therapeutics, Dublin, Ireland; 3Royal College of Surgeons in Dublin, Ireland, Ireland; 4Western University Schulich School of Medicine & Dentistry, London, ON, Canada; 5Western University Division of Nephrology, London, ON, Canada; 6Saint James’ Hospital, Dublin, Ireland.

Background: Inherited kidney diseases (IKD) are increasingly identified in adult patients. Here we demonstrate the diagnostic and clinical impact of evaluating patients with IKD in a dedicated IKD clinic (IKDC) utilising various genomic testing technologies (whole-exome sequencing, comprehensive gene-panel, and dedicated MUC-1 sequencing) and immunostaining.

Methods: We undertook a prospective cohort study of adult patients referred to an academic medical centre with suspected monogenic cause as part of the Irish Kidney Gene Project (IKGP), between 2014 and 2020. Patients with chronic kidney disease (CKD) who had either a positive family history, extrarenal features, or had CKD of “unknown cause” (uCKD) were recruited from various centres across Ireland. We attempted to identify disease-causing variants and to assess the impact of the IKDC from diagnostic and clinical perspectives.

Results: During this period, genetic testing was performed for 677 adults (n= 501 families). The median age was 53 years (range, 18-93 years) and 73.9% participants had reported a family history of renal disease. We achieved a molecular diagnostic rate of 54% (n= 374/697). Among the identified disease-causing variants, PKD was the largest cohort (n= 183, 47.8% for PKD1 and PKD2), while mutations in three other causative genes were more prevalent among the remaining identified 42 genes encompassing several Mendelian disorders; MUC-1 (n= 43, 8.1%); COL4A5 (n= 36, 7.8%); UMOD (n= 35, 7%). In the remaining 5%, the diagnostic potential of the genetic diagnosis was confirmed in 60.5% and 18% of cases were reclassified. A molecular diagnosis was established in 27 (36.5%) patients with uCKD, implying the end of their diagnostic odyssey. Clinically, a diagnostic kidney biopsy was unnecessary in 13 (77.8%) patients based on the genomic testing. 80 (47.3%) had their treatment plan altered and further 76 (45%) patients had appropriate cascade testing.

Conclusions: The IKDC is a valuable resource and the implementation of a broad range of diagnostic platforms has a direct clinical and therapeutic impact on treatment of patients with CKD.
Characterization of Patients with Alport Syndrome in the United States: A Retrospective Analysis of Medical Claims

Baris Deniz,1 Aparna Singeetham,2 Ishan Goradia,3 Ashwaryaa Clarivite,2
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Background: Alport syndrome (AS) is a rare, hereditary genetic condition that often results in chronic kidney disease and may lead to early onset of end-stage kidney disease. The prevalence estimate in the literature is around 30,000–60,000 in the US. However, there are challenges with AS diagnosis (i.e. underdiagnosis and misdiagnosis), hence real-world patient population with AS diagnosis can be less than the prevalence estimates. This study is a retrospective analysis of medical insurance claims aimed to get a real-world estimate of the number of patients with a formal diagnosis of AS in the US, their disease characteristics, and treatment patterns.

Methods: A retrospective, observational cohort analysis was conducted, that leveraged DRG/Clarivate medical claims database, that integrates multi-payer and multi-plan data and covers >220 million annual patients in the US. Patients with at least one ICD-10 code (Q87.81) designated for AS in their medical history between October 2015 to September 2020 were considered diagnosed AS cases. Characteristics of patients and prescription data were analyzed descriptively. Patient interactions with health care professionals (HCP) within the last 24 months of the study window (i.e. October 2018 – September 2020) were used to determine the primary HCP responsible for patient management.

Results: The analysis identified total of 10,387 patients with at least one AS diagnosis code. Of the 42% of the population for whom chronic kidney disease (CKD) stage data were available, 44% had advanced CKD (IV & V). Adult or pediatric nephrologists were the primary HCPs for 59% of patients. Based on the prescription data, 21.6% (2,244 patients) were prescribed ACEs/ARBs, and 10.6% (1,101 patients) were prescribed CYP3A4 inhibitors.

Conclusions: The number of patients our study identified with AS diagnosis is lower than the commonly cited prevalence estimates in the US. The discrepancy can be explained by the fact that the database used covers a majority of but not the whole US population, and our study relies on real-world diagnoses.

Funding: Commercial Support - Reata Pharmaceuticals

PO1297

Utilization of Broad-Panel Genetic Testing for Collagen Disorders of the Basement Membrane Disorders in Patients Requiring Kidney Transplantation

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Background: Patients with advanced chronic kidney disease (CKD) are often misdiagnosed. Etiology of end-stage kidney disease (ESKD) significantly impacts the selection of candidates and donors for kidney transplant (KT), and post-KT management. Identification of a genetic etiology can reclassify disease and alter KT planning. Collagen disorders such as Alport syndrome present with heterogeneous phenotypes. However, a recently proposed classification system incorporates genetic variants into the diagnosis of this disease.

Methods: Twenty-two pre- and post-KT patients with a median age of 33 years (range: 26-67 years), completed genetic testing with RenasightSM (a NGS-based >380-gene kidney panel), between June 2020 and April 2021. Test results related to COL4A4 were correlated to clinical histories, including biopsy (when available), ultrasound results, presence of proteinuria and hematuria, demographic factors, family history and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on renal diseases.

Results: Pathogenic or likely pathogenic variants in a type IV collagen gene were identified in 18.2% (4/22) of patients. All four patients had progressed to ESKD at the time of testing. One patient, with a variant in COL4A4, had a right nephrectomy and subsequently developed nephrotic range proteinuria. The second patient, with a variant in COL4A4, had genetic testing after a living related KT; the donor was subsequently referred for genetic counseling. The third and fourth individuals, brothers with a family history of CKD, for which the same familial COL4A4 variant was identified, were both carriers of the APOL1 G1 risk allele. One brother had biopsy-proven FSGS and did not respond to steroids.

Conclusions: Broad panel testing enables the identification of monogenic causes of CKD that can impact the selection of KT candidates and post-KT management.

Healthcare Resource Utilization by Patients with Alport Syndrome in the United States: A Retrospective Claims Analysis

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Background: Alport syndrome (AS) is a rare and serious inherited form of chronic kidney disease (CKD) affecting as many as 60,000 persons in the US. In severe cases, patients develop end-stage kidney disease (ESKD) in their 20’s. The health and economic burden associated with AS has not been well-characterized in the literature. This study aims to address this evidence gap.

Methods: A retrospective claims analysis (IBMs MarketScan® Commercial Database) was conducted to assess the healthcare resource utilization (HCRT) by patients with AS in the US. Patients enrolled in a health plan for a minimum of six continuous months with at least 1 inpatient or 2 outpatient claims with the AS-specific ICD-10 code were considered to have a diagnosis of AS. Patients with AS were further segmented into CKD stages, where such information was available, to understand the impact of disease progression on HCRT. Patients with AS were age- and gender-matched to a comparator group without AS diagnosis in a 1:5 proportion. The analysis included commercial (medical and pharmacy) claims from 2015 to 2019.

Results: 851 patients with AS were identified, of which 518 also had a CKD diagnosis. The mean age was 33.3 years and 51% were males. 16.2% of patients were < 18 years old. Patients with AS required more healthcare services than the matched comparator group. 19.2% of patients with AS and CKD had at least 1 inpatient admission over the course of 6 months, versus 2.1% in the matched cohort; 100% had an outpatient or office visit, versus 66% in the matched cohort; 26.7% had at least one emergency department visit, versus 6.6% in the matched cohort. The rate of HCRU increased with the increasing CKD stage, the highest utilization being observed in patients with advanced CKD. Approximately 25% of patients with AS were prescribed RASi’s, which is a commonly used treatment in eligible patients with AS.

Conclusions: Patients with AS were observed to utilize inpatient, outpatient, and emergency department services at higher rates than the comparator group, with high utilization largely driven by late-stage CKD. Consequently, delaying or preventing kidney disease may substantially reduce healthcare expenditures among patients with AS, particularly among patients with ESKD.

Funding: Commercial Support - Reata Pharmaceuticals Inc

Genotype-Phenotype Analyses in Korean X-Linked Alport Syndrome: A Multicenter Study

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Background: X-linked (XL) inheritance, caused by COL4A5 mutation, is most common in Alport syndrome (AS). Many clinical studies have elucidated the correlation between genotype and phenotype in male XLAS, whereas no association has been found in female XLAS. Here, we analyzed genotype-phenotype correlation in Korean XLAS.

Methods: This multicenter, retrospective study collected XLAS cases who has been diagnosed from 1985 to Jan 2021 in 13 tertiary centers of Korea. Sanger or next-generation sequencing were conducted in clinically suspected AS patients (male:female 96:42 from 121 Korean families) for genetic confirmation. We divided the cases into male (n=96) and female (n=4) cohorts according to the mutant types, and compared the clinical characteristics, and treatment patterns.

Results: 96 male patients (median age of presentation was 5.1 years) and 4 female patients (median age of presentation was 12 years) were analyzed. 196 patients according to mutant types, but kidney survival rate was worse for all variant types, especially for COL4A5 mutations (n=46); 2splicing mutations (n=12); 3frameshift or nonsense mutations (n=38). Kidney survival was compared between the groups using Kaplan-Meier method.

Conclusions: There were strong genotype-phenotype correlation in male Korean XLAS. Both male and female XLAS showed similar results consistent with previous papers according to mutant types, but kidney survival rate was worse for all variant types, despite the appropriate use of RASi. These data could potentially be helpful of counseling patients with XLAS.
PO1299

Sparsentan, the Dual Endothelin Angiotensin Receptor Antagonist (DEARA), Improves Kidney Function and Life Span and Protects Against Hearing Loss in Alport Mice with Developed Renal Structural Changes

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Background: In Alport syndrome (AS), endothelin type A receptor activation is an important mediator of renal and inner ear pathologies. Sparsentan (SP) administered to COL4A3 -/- mice (AS mice) in prevention mode delayed increases in proteinuria, renal structural changes and hearing loss (HL). Whether these effects translate into preservation of glomerular filtration rate (GFR), increased lifespan (LS) and protection from HL in mice where renal pathology has initiated is unknown.

Methods: Wild type (WT) and AS mice were gavaged daily with vehicle (WT-V or AS-V), 60 or 120 mg/kg SP (AS-SP60 or AS-SP120) starting at 4 weeks (W) of age or at 5, 6 or 7W. Baseline and 10W glomerulosclerosis (GS) were evaluated in kidney sections from WT and AS-V, AS-SP60 or AS-SP120 mice treated from 4W. The auditory brainstem response (ABR) was used to assess hearing. Evaluation of renal pathology in AS-SP120 11±3Travere Therapeutics Inc, San Diego, CA

Conclusions: Sp peripherally prevented the decline in GFR in AS mice, extends LS and prevents noise-induced HL even in mice with developed renal structural changes. If these results are translated successfully into the clinic, SP may offer a novel treatment approach for both renal injury and protecting hearing in AS.

Funding: Commercial Support - Travere Therapeutics

PO1300

Interim Analysis of the EAGLE Trial: An Open-Label Study to Assess the Long-Term Safety and Tolerability of Bardoxolone Methyl in Patients with Alport Syndrome

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Background: Alport syndrome is a rare genetic disease affecting up to 60,000 persons in the US.

Methods: EAGLE (NCT03749447) is an ongoing, international, multi-center, open-label, extended access trial evaluating the longer-term safety and tolerability of bardoxolone methyl ( bardoxolone) in patients with Alport syndrome who completed a prior qualifying clinical trial (CARDINAL Phase 2 and 3; NCT03019185). At baseline, patients were 12 to 70 years old with eGFR 30 to 90 mL/min/1.73 m² and UACR ≥ 3500 mg/g. Patients receive bardoxolone daily and dose is escalated up to 20 mg or 30 mg (for patients with UACR > 300 mg/g).

Results: As of data cutoff (01/18/2021), 96 patients were enrolled in the EAGLE study, including 79 patients from CARDINAL Phase 3 (placebo: n=46, Bard: n=33), and 17 patients who received Bard in CARDINAL Phase 2. Mean age was 42 years, and 8 (8%) patients were <18. At baseline, mean eGFR was 58.2 ± 21.4 mL/min/1.73 m² and mean UACR was 183 ± 40 mg/g. Increases in eGFR were seen in patients who previously received placebo and initiated Bard treatment in EAGLE. Patients who previously received Bard for two years in CARDINAL also continued to experience mean eGFR increases in their third year of treatment. Bard has generally been well tolerated, with no deaths or drug-related severe adverse events (SAEs) reported in EAGLE to date. No drug-related SAEs were reported and no changes in blood pressure were observed. Nearly all (94%) adverse events were mild to moderate.

Conclusions: In EAGLE, Bard increased eGFR in patients with Alport syndrome, and increases observed in CARDINAL were sustained in the third year of treatment. To date, the longer-term safety profile of Bard is similar to that observed in the CARDINAL trial.

Funding: Commercial Support - Reata Pharmaceuticals

PO1301

Integrated Analysis of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

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Background: Alport syndrome is a rare and serious inherited form of CKD. An integrated analysis of efficacy and safety was conducted from the CARDINAL Phase 2/3 (NCT03019185) and EAGLE (NCT03749447) trials of bardoxolone methyl (Bard) in patients with Alport syndrome.

Methods: THE CARDINAL Phase 2 trial was open-label and enrolled 30 patients ages 12 to 60 years with Alport syndrome, baseline eGFR values 30 to 90 mL/min/1.73 m² and UACR ≥ 3500 mg/g. CARDINAL Phase 3 was an international, multi-center, double-blind, placebo-controlled trial with similar eligibility criteria and randomized 157 patients. EAGLE is an ongoing, open-label, extended access trial that is enrolling patients who completed CARDINAL Phase 2/3 trials.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: A total of 218 patients were included in the analysis (placebo: n=80, Bard: n=138). A majority (61%) of patients were female and receiving renin-angiotensin-aldosterone system inhibitor (83%). Mean age was 40 years, and 31 (14%) patients were <18 years old. Mean baseline eGFR was 60.4 and 62.3 mL/min/1.73 m² and the maximum duration of exposure was 3.2 and 1.9 years for Bard and placebo groups, respectively. The Bard group had significant increases in eGFR from baseline at the last on-treatment assessment (mean±SE: 3.37±1.21 mL/min/1.73 m²; p<0.006). Significant decreases in eGFR were seen in the placebo group (mean±SE: -8.30±1.58 mL/min/1.73 m²; p<0.0001), resulting in a significant difference between groups after treatment withdrawal (p<0.03 vs placebo). Consistent with prior studies, common adverse events (AE) included muscle spasms, aminotransferase increases, and hyperkalemia. Discontinuations due to AEs were uncommon (9% of Bard and 5% of placebo groups). Across all studies, no major cardiac events were observed and no changes in blood pressure were observed.

Conclusions: Consistent with individually reported prior trials, an integrated Alport syndrome analysis set showed that Bard preserved kidney function with significant on- and off-treatment eGFR benefits and was generally well tolerated by patients.

Funding: Commercial Support - Reata Pharmaceuticals

PO1302
Novel Keap-Nrf2 Protein-Protein Interaction Inhibitor UBE-1099 Ameliorates the Severity of Experimental Alport Syndrome
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Background: Bardoxolone methyl is an electrophilic agent that induces Nrf2 activation by irreversibly and covalently binding to the cysteine residue of Keap1. Bardoxolone methyl has been shown to improve glomerular filtration rate (GFR) in clinical trials, and is attracting attention as a novel agent for chronic kidney disease. However, there is concern about long-term efficacy due to the unknown mechanism of GFR improvement and transient increase in albuminuria. Moreover, irreversible Keap1 inhibitors such as Bardoxolone methyl may covalently bind to other proteins in a non-specific manner and induce side effects due to off-target activities.

Methods: We developed a reversible Keap1 inhibitor that inhibits Keap1-Nrf2 protein-protein interaction (PPI) and evaluated its efficacy using Alport syndrome mice model (Col4a5-G5X). Development of Keap1-Nrf2 PPI inhibitor was performed by fluorescence polarization and Nqo1 induction test. The obtained novel compound UBE-1099 (30 mg/kg/day) and CDDO-Im (3, 10 mg/kg/day; rodent tolerable Bardoxolone methyl analogue) were orally administrated to Alport mice and efficacy was evaluated.

Results: UBE-1099 showed higher Nqo1 induction efficiency compared with CDDO-Im in mouse renal tissue. While CDDO-Im only improved inflammation pathology in Alport mice, UBE-1099 uniformly improved renal function (GFR and Plasma creatinine, but not albuminuria), podocyte injury, glomerulosclerosis, inflammation and fibrosis. Moreover, UBE-1099 treatment significantly prolonged the lifespan of Alport mice.

Conclusions: This study firstly revealed the efficacy of Keap1-Nrf2 PPI inhibitor for glomerulosclerosis. We will elucidate next the mechanism of renal pathology improvement, which may provide useful information for Nrf2 activators including bardoxolone methyl for clinical application.

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PO1303
Patient Global Impression of Change in Patients with Alport Syndrome in the CARDINAL Phase 3 Trial
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Background: Alport syndrome is a rare and serious inherited disorder of the kidneys affecting as many as 60,000 persons in the US with no specific therapies approved for its treatment.

Methods: An international, multicenter, double-blind, placebo-controlled, randomized Phase 3 trial (CARDINAL; NCT03019185) evaluated the safety and efficacy of bardoxolone methyl (Bard) in patients with Alport syndrome 12 to 70 years of age with baseline eGFR 30-90 mL/min/1.73 m² and UACR ≥ 3500mg/g. As an exploratory endpoint, the trial assessed patient global impression of change (PGIC), a non-disease specific 7-point scale that asks patients to rate how much their illness has changed as very much/much/minimally improved (1, 2, and 3 points), no change (4 pts), or minimally/much very much worse (5, 6, and 7 pts) after 48 and 100 weeks of treatment.

Results: A total of 157 patients were randomized to Bard (n=77) or placebo (n=80). In addition to significant on-treatment and off-treatment increases in mean eGFR relative to placebo (between-group differences of 7.7 ± 2.1 [p=0.0005] at Week 100 and 4.3 ± 1.9 mL/min/1.73 m² [p=0.023] at Week 104, respectively), Bard improved PGIC scores relative to placebo (lower values) after 48 and 100 weeks. Categorical summaries also showed more patients randomized to bardoxolone (34%) reported their condition had improved compared to those on placebo (19%) after 100 weeks of treatment.

Conclusions: In CARDINAL, Bard significantly improved eGFR in patients with Alport syndrome and also resulted in improvements in how patients evaluated their wellbeing.

Funding: Commercial Support - Reata Pharmaceuticals

PO1304
Treatment with Antisense-Oligonucleotide or Splicing Regulating Proteins for X-Linked Alport Syndrome Cases with Deep Intronic Variant
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Background: X-linked Alport syndrome (XLAS) is a hereditary progressive renal disease caused by mutation in COL4A5. Some cases of XLAS are caused by deep intronic variants which cause aberrant splicing and produce cryptic exon inclusion. Preventing translation of such cryptic exon has the potential to be an effective therapy. We reported that exon skipping therapy with antisense-oligonucleotide (ASO) was very effective in the XLAS mice model with a truncating mutation. However, an ASO needs very high sequence specificity and few patients can be treated by the same ASO. Therefore, we attempted to modify the splicing pattern not only by ASO but also by proteins important for splicing regulation. U2A6F5 is one of the important splicing related proteins binding to polypyrimidine tracts promoting exonization. It has been reported that overexpression of the U2A6F5 promotes or suppresses exonization in some circumstances.

Methods: We identified four cases of XLAS caused by the presence of the same cryptic exon inclusion (c.384_385ins538-385-385(67)1) by different deep intronic variants: three cases (c.385-756C>G, c.385-749T>A and c.385-645T>A) were ours and 1 (c.385-719G>A) was a reported variant. For these cases, we introduced ASO that could skip cryptic exon. Moreover, using in vitro splicing evaluation system (minigene assay), we attempted to reduce the expression of cryptic exon by overexpression of U2A6F5.

Results: We succeeded in preventing the cryptic Exon insertion by introducing ASO treatment for patient’s urine derived cells. In addition, in all patients, overexpression of U2A6F5 in the minigene splicing analysis system successfully reduced the cryptic exon inclusion.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1305
Small Molecule APOL1 Inhibitors Block APOL1 Pore Function and Reduce Proteinuria in an APOL1-Mediated Kidney Disease Mouse Model
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Background: Two genetic variants of APOL1 (G1 and G2) are associated with increased risk of kidney diseases. Current treatment options for APOL1-mediated kidney diseases are limited and do not address the underlying cause of disease. Here, we report the discovery of a series of novel small molecule APOL1 inhibitors, including the clinical candidate VX-147, that block APOL1-mediated cell death and ion flux. In addition, activity on APOL1 biological function was assessed using a trypanosome viability assay. Finally, changes in proteinuria following APOL1 inhibitor administration were assessed using a transgenic mouse model homozygous for the APOL1 G2 variant (G2ap50).

Results: Small molecule APOL1 inhibitors showed binding to all three forms of APOL1 (wild-type, G1 and G2 variants). In cellular assays, APOL1 inhibitors prevented APOL1-mediated HEK293 cell death and inhibited APOL1-mediated ion flux. Addition of APOL1 inhibitors to trypanosome cultures rescued the parasites from APOL1-induced killing. The potency of VX-147 was consistent across the in vitro functional assays described above (IC50 of approximately 2nM). Finally, administration of an APOL1-dependent proteinuria in an APOL1-mediated transgenic mouse model of kidney diseases. Taken together, our results strongly suggest small molecule APOL1 inhibitors, such as VX-147, target the underlying cause of disease, and have the potential to treat APOL1-mediated kidney diseases.

PO1306
Inhibition of Endoplasmic Reticulum Stress Signaling Rescues Cytotoxicity of Human APOL1 Risk Variants in Drosophila
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Background: Renal risk variants of the APOL1 gene are associated with severe kidney disease, putting homogenous carriers at risk. APOL1 G1- and G2-alleles likely represent gain-of-function (GOF) mutations as human subjects with APOL1 null alleles have been found to be without renal anomalies. A wide range of mechanisms that are frequently in conflict have been described for APOL1-associated nephropathies.

Methods: The genetic tool-kit in Drosophila allows unique in vivo insights into disrupted cellular homeostasis. To perform a mechanistic analysis in this model, we expressed APOL1 control and the GOF renal risk variants in the podocyte-like Drosophila nephrocytes and a wing precursor tissue. Results: APOL1 risk variant expression entailed elevated endocrine function of garland cell nephrocytes while processing of endocytic cargo and slit diaphragm morphology remained unimpaired. All APOL1 variants located to the endoplasmic reticulum (ER) and electron microscopy revealed significantly elevated ER swelling upon expression of risk variant G2-APOL1, indicating stimulation of ER stress. We employed Drosophila wing precursor tissue since this epithelial model enables unique recording of relative changes side by side within the same animal to study ER stress. Overexpression of the renal risk variants G1 and G2 caused a markedly stronger upregulation of PDI and apoptosis, while expression of wildtype APOL1 resulted in milder upregulation. As a control, ER stress was absent upon deletion of 9 aa in the BH3 domain in the G2-APOL1 construct. We further confirmed APOL1-dependent ER stress by detection of chaperone induction and an Xbp1-reporter in the wing precursor. Both, genetic and pharmacological inhibition of ER stress abrogated apoptosis identifying ER stress as the essential factor of APOL1-induced cytotoxicity. This represents the first rescue of APOL1-associated cytotoxicity in vivo. Direct ER stress induction in nephrocytes phenocopied APOL1 risk variant expression, supporting that ER stress underlies the gain-of-function in nephrocytes.

Conclusions: Our data reveal ER stress as the essential consequence of APOL1 risk variant expression in vivo, indicating this pathway’s central role in the pathogenesis of APOL1-associated nephropathies.

PO1307
A Cohort Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) Started on SGLT2 Inhibitors
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Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to slow estimated glomerular filtration rate (eGFR) decline in chronic kidney disease (CKD) but have not been tested in patients with ADTKD. We performed a prospective nested cohort observational study and analyzed changes in eGFR and kidney injury marker 1 (KIM-1) in patients who were prescribed SGLT2i by their physicians.

Methods: We obtained baseline and follow-up laboratory studies at 1 week, 1 month, and 4 months after starting an SGLT2i and compared eGFR with baseline function. We also obtained information about adverse events.

Results: 12 individuals were started on SGLT2i by their physicians, with 10 on empagliflozin, 2 dapagliflozin. Table 1 shows the changes in eGFR and KIM-1. For patients with eGFR > 30, mean eGFR increased at 1 month by 3 ml/min. At four months, eGFR was 3 ml/min below baseline (-18.5% due to low baseline eGFR). For eGFR > 30, eGFR decline was 12% from baseline at one month and 8% from baseline at 4 months. Plasma KIM-1 was unchanged, but urinary KIM-1 increased by 100%. One patient stopped empagliflozin at his request after 8 weeks due to decline in eGFR of 14% from baseline. No other adverse events noted. Two patients have been treated for 6 months with stable eGFR.

Conclusions: The change in eGFR after treatment with SGLT2i was consistent with prior studies of CKD. The plasma KIM-1 was unchanged, but the rise in urinary KIM-1 was very concerning. Further study is required to determine if these agents are beneficial in ADTKD. An additional 4 months of follow up will be presented at ASN.

Funding: NIDDK Support, Private Foundation Support

*Mean was computed as the average change in eGFR for each individual (at time point), compared to their baseline measurement.

PO1308
A Prospective Observational Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
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Background: GFR decline in ADTKD due to UMOD or MUC1 mutations has not been well characterized. We have begun an international prospective cohort study to determine genetic and environmental factors associated with progression. We report here on early recruitment.

Methods: Patients with positive genetic testing for UMOD or MUC1 mutations prior to transplantation or starting dialysis are eligible. A baseline collection of health information, serum and urine biomarkers will be performed, with patients then followed longitudinally, with a serum creatinine measurement performed three times per year. There will be a nested cohort of study women who develop pregnancy during the study and patients started on ACE inhibition.

Results: Since March 2021, we have enrolled 57 patients in the prospective observational study, with 20 men, 35 women. The mean age of patients is 43.3 years, the mean baseline eGFR is 39.96 ml/min/1.73m2. Table 1 shows baseline characteristics of patients enrolled in the study. No patients with CKD Stage 1 or 2 suffered from HTN, and only 39% of patients with CKD Stage 3 had HTN. Only 18% of patients were receiving ACE/ARB inhibition.

Conclusions: Despite significant CKD, there was a relatively low prevalence of HTN. Only 18% of patients were receiving ACE inhibition, indicating a potential therapeutic intervention. Please contact us if you have a patient who may be interested in participating in this prospective study (tablever@wakehealth.edu).

Funding: NIDDK Support, Private Foundation Support

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Baseline Characteristics of Enrolled ADTKD Patients

PO1309

Vasopressin Induces Urinary Uromodulin Secretion by Activating Protein Kinase A

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Background: Urinary uromodulin, secreted by renal tubular cells, protects against urinary tract infections (UTIs) and kidney stones. In contrast, the intracellular accumulation of uromodulin is associated with hypertension and chronic kidney disease (CKD). In addition, uromodulin gene mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-UOMD) via abnormal intracellular accumulation of uromodulin. However, the physiological stimuli for urinary uromodulin secretion remain largely unknown.

Methods: We investigated the acute effect of vasopressin/cAMP signaling on urinary uromodulin secretion in mice and in kidney epithelial cells stably expressing uromodulin. Additionally, we assessed the effect of vasopressin/cAMP signaling in kidney epithelial cells stably expressing mutant uromodulin, which causes ADTKD-UOMD.

Results: Desmopressin, a vasopressin type 2 receptor agonist, dramatically increased short-term tubular uromodulin secretion in mice. Immunofluorescence studies and ultracentrifugation-based polymerization assay suggested that desmopressin induced intracellular polymorphic filaments of uromodulin, indicating physiologically functional secretion. As a result of increased excretion, uromodulin abundance in the murine kidney was clearly reduced by desmopressin. In the cellular model, apical uromodulin secretion was increased in response to vasopressin/cAMP signaling, consistent with in vivo experiments. We also demonstrated that the response was dependent on cyclic AMP-dependent protein kinase (PKA) signaling pathway. We further showed that cAMP signaling induced excretion of mutant uromodulin. cAMP signaling suppressed PERK phosphorylation, which was upregulated by mutant uromodulin. cAMP signaling induced cytoprotective effects.

Conclusions: Our work revealed vasopressin/cAMP/PKA signaling as a physiological stimulus of urinary uromodulin secretion. This finding may provide the basis for novel treatment strategies for UTIs, kidney stones, and potentially hypertension, nephrolithiasis, and nephrocalcinosis. This disease is caused by inactivating mutations in the CLOC5 gene, which encodes the voltage-gated CIC-5 chloride/proton antipporter. CIC-5 is expressed predominantly in the kidney and participates in the acidification of proximal tubule endosomes. Currently, the treatment of DD1 is only supportive and focused in delaying disease progression. Our group has generated a Clocn5 knock-in (KI) mouse that presents the main clinical manifestations of DD1 and carries the pathogenic mutation p.V232del, which causes partial CIC-5 retention in the endoplasmic reticulum. Here, we aimed to assess the ability of sodium tripolyphosphate (4-PBA), a small chemical chaperone, to ameliorate DD1 symptoms in this mouse model.

Methods: Twelve-weeks old male Clocn5 KI mice (n=50) and WT (n=33) littermates were divided into 2 groups, one was treated with 250 mg/kg/day of 4-PBA in drinking water for 30 days, whereas the other group was given water without the drug for the same amount of time. Mice were placed in metabolic cages before and after treatment for 24h. Urinary β2-microglobulin and serum and urinary creatinine were measured by ELISA. Calcium and phosphate concentrations in urine were estimated using colorimetric kits. Water intake and food intake and 24-h urinary excretion were also measured, and mouse body weights were monitored.

Results: We observed a significant reduction of β2-microglobulin urinary excretion in KI mice treated with 4-PBA compared to non-treated animals (p<0.0004). Glomerular filtration rate was also improved in treated mice (p=0.03). Urinary production, urinary calcium, and phosphate levels did not differ compared with non-treated mice.

Conclusions: 4-PBA reduces LMPB in Clocn5 KI mice, suggesting that this treatment could represent a promising therapeutic option for some DD1 patients.

Funding: Government Support - Non-U.S.

PO1312

Long-Term Efficacy of Migalastat on Renal Function and Outcomes in Patients with Fabry Disease (FD)

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Background: FD, caused by pathogenic GLA variants leading to functional deficiency of α-galactosidase A (α-Gal A), can eventually result in key organ damage. Preserving renal function and preventing Fabry-associated clinical events (FACEs) are important treatment goals. Approved therapies include enzyme replacement therapy (ERT) and the pharmacological chaperone migalastat. Stabilized renal function and FACE occurrence up to 30 mo have been reported in migalastat-treated adults with amenable GLA variants; here, we extend these analyses up to 8.6 yrs.

Methods: Integrated data from phase 3 clinical trials (FACETS, NCT00925301; ATTRACT, NCT01218659) and open-label extension studies (NCT01458119; NCT00925185) were used to evaluate the eGFR slope using linear regression in pts treated with migalastat for 22 yrs (n=78). Incidences of FACEs (predefined renal, cardiac, and cerebrovascular events) were assessed in all pts (N=97). Analyses were stratified prior treatment and phenotype. Cox regression modeling was used to identify predictors of FACE occurrence.

Results: eGFR remained stable for both ERT-naive and ERT-experienced pts who received migalastat for 22 yrs (median [min-max] duration: 5.9 [2.0-8.6]); the mean (SD) annualized rates of change in eGFR (mL/min/1.73 m²) were -1.6 (3.1) and -1.6 (3.6), respectively. In male pts with the classic phenotype (classification based on multigorgan involvement and [ERT-naive only] α-Gal A level at baseline; n=25), mean (SD) rate of change in eGFR was -2.2 (4.4) mL/min/1.73 m², eGFR was also analyzed by baseline renal function and proteinuria levels. In all migalastat-treated pts (median duration: 5.1 yrs), the incidence of composite FACEs (per 1000 patient-years) was 48.3 (65.3 for...
classic males) and incidence of renal events was 4.4 (14.5 for classic males). Lower baseline eGFR and FACES in classic males vs all others; however, rate of renal events was too low to analyze predictors.

Conclusions: Results demonstrate long-term efficacy of migalastat in stabilizing eGFR in pts with FD, including male pts with the classic phenotype. FACES incidence in pts receiving migalastat compared favorably to historic reports of ERT. The inverse correlation of eGFR with FACES suggests the importance of early diagnosis and treatment to preserve renal function.

Funding: Commercial Support - Amicus Therapeutics, Inc.

POI1313

Twenty-Year Renal Prognosis in Patients with Fabry Disease Who Underwent Enzyme Replacement Therapy

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Background: The relationship between long-term renal prognosis and renal histopathology after enzyme replacement therapy (ERT) for Fabry disease (FD) has not been fully investigated.

Methods: Nine patients with FD from our hospital who had participated in a Japanese phase 2 study (August 2000–May 2001) on agalsidase β were eligible for this case-control study. They underwent repeated renal biopsy (before and six months after agalsidase β treatment), and the intra-renal amount of globotriaosylceramide (GL3) was measured at the same time points. Clinicopathological features were compared between the groups with or without developing end-stage kidney disease (ESKD).

Results: Seven patients were included in this study. Among them, two were lost to follow-up. All were males, with a median age at the start of treatment of 30 [quartile 24.5, 31.5] years, and median serum creatinine level (s-Cr) of 1.1 [1.0, 1.2] mg/dL. The podocyte score (International Study Group of Fabry Nephropathy score system) improved in all patients after ERT from that evaluated before ERT. Intersitial fibrosis/tubular atrophy (IF/TA) worsened in three patients. The proportion of foamed tubules improved in five patients. Intra-renal accumulation of GL3 decreased six months after ERT in all patients. All patients continued to receive agalsidase β or agalsidase α after the phase II study. While seven patients developed ESKD (median 6.7 years), three patients showed no exacerbation of renal function. The s-Cr level, age, and urinary protein excretion at the start of ERT were higher in the ESKD group. The decrease in the intra-renal accumulation of GL3 was not significantly different between the two groups, but the proportion of foamed tubules in the first biopsy and the degree of IF/TA in the second biopsy were higher in the non-ESKD group compared with the ESKD group. We found that the non-ESKD group had a lower baseline eGFR and a higher s-Cr level than the ESKD group. The difference in the expression of IF/TA was observed in all patients.

Conclusions: This study suggests that tubulointerstitial injury has a crucial role in the determination of renal prognosis and that earlier diagnosis and intervention in patients with FD may improve the renal prognosis. Further studies are needed on the relationship between tubulointerstitial injury and GL3 accumulation.

POI1314

Systems Analyses of Fabry Renal Transcriptome and Its Response to Enzyme Replacement Therapy (ERT) Identifies a Cross-Validated and Drugable ERT-Resistant Module

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Background: Fabry nephropathy (FN) is a rare disorder caused by mutations in the alpha-galactosidase A gene that can, to a certain degree, be managed with enzyme replacement therapy (ERT). Via understanding the molecular basis of FN and ERT's long-term impact, we aim at providing a framework allowing selection of biomarkers and drug targets.

Methods: Obtained from controls and two independent FN-cohorts, mRNA-isolates from archival kidney biopsies taken prior and up to 10 years of ERT, were subjected to RNAseq. Combining pathway-centered analyses with network-science allowed to estimate their suitability as biomarkers and potential targets for adjunct treatment.

Results: Combining transcriptional landscapes comprehensively reflected differences in FN-cohort characteristics. With the exception of few key aspects, in particular concerning arteries, early ERT in classical Fabry patients could lastingly revert FN kidney-compartment's molecular state to closely match N. CTRs. Thus, we identified and cross-validated ERT-resistant modules that, when leveraged with external data, allowed estimating their suitability as biomarkers and potential targets for adjunct treatment.

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POI1315

Resistant Focal Segmental Glomerulosclerosis (FSGS) due to Leci-thin-Colesterol Acyltransferase (LCAT) Deficiency: Is Early Gene Testing the Answer?

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Introduction: LCAT deficiency is a rare autosomal recessive disorder due to mutations in the LCAT gene presenting with corneal opacities, anemia, proteinuria, reduced HDL and CKD with progression to ESKD by the 4th–5th decade. Electron microscopy (EM) is characteristic for abundant partially electron-dense and lucent deposits in the mesangium and basement membrane. Late diagnosis is not uncommon due to its rarity and nonspecific presentations in the early stages. Here we report a case of therapy resistant FSGS later uncovered as LACT deficiency confirmed by gene tests.

Case Description: A 49-year-old male presented to genetic nephrology clinic in 2020 with a clinical diagnosis of LCAT deficiency. In 2007, he had presented with hematuria, proteinuria with a serum creatinine of 2.4mg/dL, Hb 11 g/dL, albumin 2.4g/dL, total cholesterol 416mg/dL, HDL 14mg/dL and urine protein of 8.9g/d. Urine microscopy showed fine granular casts and dysmorphic RBCs. Kidney biopsy revealed FSGS with moderate tubulointerstitial fibrosis. EM showed some unexplainable intramembranous podocyte lesions and subendothelial thickening, which were thought to be sequelae of prior immune mediated membranous glomerulonephritis. Patient failed treatment with months of steroids, oral cyclophosphamide and mycophenolate. Repeat biopsy in 2010 showed worsening of the prior findings. In 2011, corneal deposits led to a suspicion of LCAT deficiency. He progressed to ESKD in 2011 and kidney transplant in 2020. Genetic testing disclosed a homozygous nonsense variant c.321C>A (p.Tyr107*) in LCAT gene. A thorough genetic counseling included risk for his siblings and graft recurrence.

Discussion: LCAT deficiency can present with resistant or atypical appearing FSGS. This case emphasizes the need of early genetic assessment on suspicious biopsies or therapy resistant FSGS cases to timely diagnose and avoid unnecessary immunosuppression.

POI1316

ESKD due to Primary Hyperoxaluria Type I

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Introduction: Primary hyperoxaluria type I (PH1) is a rare autosomal recessive disease (less than 3 cases per million population). Nephrolithiasis and nephrocalcinosis lead to progressive renal impairment and subsequent oxalate deposition in various tissues. We present a case of PH1 diagnosed late in life and ultimately requiring definitive management with liver-kidney transplant due to rapid progression to end stage kidney disease.

Case Description: 55 year old male with history of renal calculi at birth, recurrent nephrolithiasis and PHT1 was hospitalized for acute kidney injury following 2 weeks of nausea and poor intake. His admission serum creatinine (Scr) was 11 from baseline of 3.5 four months before. He was diagnosed with PHT1 eight months prior via urinary oxalate measurement and genetic testing. He was started on low oxalate diet, calcium carbonate 1000mg with meals and pyridoxine 500mg daily. Ultrasound at admission notable for...

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diffuse increased echogenicity and bilateral non-obstructing calculi. Initial serum oxalate level was 63.5micromol/L and 24 hour urine oxalate level was 116mg/24hrs. Ser failed to improve with intravenous fluid administration and renal replacement therapy was initiated with goal serum oxalate level of <30micromol/L. Hemodialysis was performed daily for four hours with high flux membrane. Serum oxalate levels improved to nadir of 40micromol/L. Definitive therapy with simultaneous liver-kidney transplant was ultimately pursued.

Discussion: Our patient required intensive hemodialysis while awaiting liver-kidney transplant following late diagnosis of PH1 and development of end stage kidney disease. Early diagnosis is key to reduce morbidity and mortality. Progressive kidney impairment leads to inability to excrete the increased oxalate produced by the liver and subsequent systemic deposition of oxalate including in the kidney causing multiorgan dysfunction. Hemodialysis removes oxalate but it is difficult to consistently reduce serum oxalate levels below goal given continued production of oxalate and rebound. Early treatment options include a trial of pyridoxine, hyperhydration, low oxalate diet and novel RNA inhibitors.

PO1319

Modeling the Risk of Progression to Kidney Failure in Patients with Primary Hyperoxaluria type 1 Treated with Lumasiran Relative to a Natural History Cohort Not Treated with Lumasiran

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Background: In primary hyperoxaluria type 1 (PH1), the risk of kidney failure (KF) is positively associated with urinary oxalate (UOx) excretion. Lumasiran is an RNAi therapeutic to lower UOx levels in patients with PH1. We estimated the risk of progression to KF in patients with PH1 treated with lumasiran, relative to patients not treated with lumasiran.

Methods: A skewed-normal distribution of 24hr UOx values for patients with PH1 was simulated based on reported UOx values from the Rare Kidney Stone Consortium (RKSC) PH Registry among patients who were not in KF at diagnosis and did not receive lumasiran. Data from the ILLUMINATE-A trial of lumasiran were used to build a log-linear model of post-lumasiran treatment steady-state UOx as a function of baseline UOx. The distribution of steady-state, on-treatment UOx values for RKSC patients was then predicted by applying this model to the simulated 24hr UOx values of the RKSC cohort.

Conclusions: A risk model of KF as a function of 24hr UOx excretion, based on Kaplan-Meier curves of renal survival reported from the RKSC, was used to estimate the number of KF events/100 patients in the RKSC PH1 cohort, had all received lumasiran.

Results: The mean (SD) 24hr UOx excretion for the RKSC PH1 cohort was 2.2 (1.1) mmol/24hr/1.73m2 in the absence of lumasiran treatment and was predicted to decrease to 0.62 (0.17) mmol/24hr/1.73m2 in a model that simulated the effect of lumasiran administration (Figure 1). The predicted number of KF events/100 patients (95% CI) using the model for patients not treated with lumasiran at 10, 20 and 30 years, is 10 (4, 23), 32 (19, 50), and 42 (27, 59), respectively. In the model of lumasiran treatment, the estimated cumulative number of KF events/100 patients (95% CI) was 4 (1, 12) at 10 years and remained unchanged at 20 and 30 years.

Conclusions: This analysis predicts a long-term reduction in KF risk among PH1 patients treated with lumasiran, associated with prompt treatment at diagnosis.

Funding: Commercial Support - Alnylam Pharmaceuticals

PO1318

Association Between Longitudinal Plasma and Urine Oxalate and Time-to-Kidney Failure in Primary Hyperoxaluria Using Joint Models

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Background: The association between plasma oxalate (POX), urine oxalate (UOX) and time to kidney failure (KF) in patients with the rare disease primary hyperoxaluria (PH) is challenging to study due to small sample sizes and correlations among POX, UOX, and eGFR. To develop better KF models that simultaneously account for all 3 variables we used a novel statistical approach, joint models, modeling longitudinal biomarker processes (eGFR, POX, UOX) and survival process (time-to-KF) jointly, using retrospective data from the Rare Kidney Stone Consortium PH registry.

Discussion: To jointly model longitudinal biomarker processes and survival process, we employed the joint model framework. The joint model framework allows flexible estimation of the association, which may impact conclusions. These novel methods can be used to inform patient-specific decisions about future KF risk, and the risk-benefit of novel treatment approaches.

Methods: Repeated eGFR, UOX, and POX after PH diagnosis were obtained from the registry. Time-to-KF was defined as time between PH diagnosis until transplantation, dialysis or eGFR<15 mL/min/1.73m2. A multivariate joint model was fit with longitudinal sub-models for each biomarker and a survival sub-model for KF. Longitudinal sub-models employed linear mixed effects models with biomarkers on the log scale. Joint models shared information between longitudinal and survival sub-models such that eGFR, UOX, and POX were time-dependent variables in the survival sub-model, specifically using subject-specific mean biomarker values. Models were adjusted for age and sex at diagnosis. Results were compared to last observation carried forward (LOCF) analyses.

Results: A total 166 patients (mean 5 POX and 7 UOX per patient) with 60 KF events during follow up were included. With LOCF, POX positively associated with KF risk, both unadjusted and adjusted for other biomarkers (hazard ratio (HR) = 1.14 per mmol/L, 95%CI = 1.07, 1.22, p<0.001), while UOX was not associated with KF after adjustment. With joint modeling, POX and KF were not significantly associated after adjustment (HR = 1.12, 95%CI = 0.99, 1.30, p=0.08), while higher UOX was associated with lower KF risk (HR = 0.30 per mmol/1.73m2/24h, 95%CI = 0.07, 0.92, p=0.04).

Conclusions: When modeling unevenly spaced longitudinal biomarkers and their association with KF, the LOCF time-dependent model makes implausible assumptions about steady-state biomarkers between observations. Implementation of a joint modeling framework allows flexible estimation of the association, which may impact conclusions.

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PO1320

The Complex Landscape of Factor H and Factor I Rare Variants in Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy

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Background: Complement genetics has been extensively studied to dissect the pathophysiology of atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) paving the way for highly tailored therapy. However, the assessment of each identified variant’s contribution to disease pathogenesis remains a challenge in particular for rare variants detected in patients as well as in healthy individuals in the genome Aggregation Database (gnomAD). In this study we aimed to describe the rare variants in Factor H (CHI) and Factor I (CFI) genes identified in the French cohort of patients with aHUS and C3G.

Methods: We analyzed the distribution of the allele frequency (AF) of rare variants identified in 397 and 398 adult patients with a diagnosis of aHUS without coexisting disease and with C3G/aggregated-mediated membranoproliferative glomerulonephritis (Ig-MPGN), respectively. We selected for this study variants with minor AF (MAF) below 0.1% in European healthy individuals.

Results: The frequency of patients with rare variants in CHI (108/398 vs 54/398) and CFI (33/397 vs 17/397) genes was higher in aHUS compared to C3G. A total of 148 variants were identified in CHI (n=98) and in CFI (n=50) genes. Among them, 9 were present in both diseases. We identified 43 (67%) and 20 (66%) novel variants in CHI and CFI in aHUS and C3G, respectively. Among them, 98% are pathogenic or likely pathogenic. The frequency of rare variants reported in gnomAD. The frequency of variants causing FH and FI deficiency is similarly in both diseases (70% of the variants). The frequency of CHI variants identified in more than 1 patient is increased in aHUS compared to C3G (11/64 vs 2/38). We identified 12 (12/38, 31%) and 2 (2/12, 16%) novel variants in CFI in aHUS and C3G, respectively. Reported variants in CHI are more frequent in C3G than in aHUS (10/12 vs 26/38). The frequency of variants reported in gnomAD is higher in CHI (80%) compared to CFI (14%).

Conclusions: Our study indicates that novel pathogenic rare variants in complement genes are more frequent in aHUS than in C3G. However, half of the variants reported in gnomAD have a potential impact on gene function. Our results suggest that CHI variants are more damaging than CFI variants, and may contribute more significantly to the pathogenesis of both diseases, as compared to CFI.

PO1321

Phenotypic-Genotypic Relationship of Focal and Segmental Glomerulosclerosis (FSGS)

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Background: FSGS can be of primary, secondary or genetic origin. The objective of our work is to establish in which patients with a histological diagnosis of FSGS a genetic etiology should be suspected.

Methods: The study included adult patients with a histological diagnosis of FSGS and normal albumin less than 58%. We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHS2 mutations were discovered in 7 (23%) patients. The remaining cases with normal albumin (58%). We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHS2 mutations were discovered in 7 (23%) patients. The remaining cases with normal albumin (58%).

Results: Out of 108 samples received, 80 patients met the inclusion criteria. We detected FSGS-related pathogenic genetic variants in 31 (39%) patients, finding no difference between those whose indication was steroid resistance (32 %) or proteinuria with normal albumin (58%). We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHS2 mutations were discovered in 7 (23%) patients. The remaining cases with normal albumin (58%).

Conclusions: Genetic testing should be considered in FSGS patients in which a secondary cause has been excluded, to determine the patient’s prognosis, treatment and perform familial screening.

Funding: Private Foundation Support

PO1322

Insight into the Pathophysiology of Hearing Loss and Renal Tubular Dysfunction Through Genetic Testing

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Introduction: In this case report, we present a case of Type 3b Bartter’s Syndrome associated with sensorineural hearing loss.

Case Description: A 69 year old caucasian female with a history of hypertension and osteoporosis presented to the emergency department with a worsening dry cough, altered mental status, and paresthesias. Physical examination was positive for Chvostek’s sign and hearing loss bilaterally. Laboratory analysis was significant hypokalemia, hypocalcemia, hypoparathyroidism, and nephrocalcinosis. EKG on presentation displayed significant QT prolongation (QTC of 482 ms). The patient was treated for symptomatic hypocalemia and initiated on calcium, potassium, and magnesium supplementation. 24 hour urine collection yielded: potassium and magnesium wasting and normal range calciuria. Parathyroid hormone was found to be inappropriately low in the setting of severe hypocalcemia but attributed to hypomagnesemia. Bartter’s vs. Gitelman’s was suspected, although profound hypomagnesemia suggested the latter. Renasight, a kidney gene panel employing next generation genome sequencing revealed a heterozygous variant in the basal chloride channel (CLCNKB), associated with Bartter’s Syndrome Type 3/4B. This channel is found in the stria vascularis and can lead to sensorineural deafness. Hypoparathyroidism persisted in spite of adequate Magnesium, Vit D levels suggestive of primary hypoparathyroidism of autoimmune etiology.

Discussion: The positivity of CLCNKB heterozygous mutation suggested Bartter’s Type 3/4B and this explained hearing loss and aided in the final diagnosis. Individuals who express both type A and B mutations present in infancy or antenatally. In a series of 115 patients w/ type B gene mutation, 26% had a Gitelman-like syndrome which includes loss of type 1 (1). Our case illustrated the utility of genetic testing in mixed electrolyte wasting presentations. Interestingly, the patient has persistent hypoparathyroidism for which no genetic basis was identified such as the calcium sensing receptor mutation.

Renal Studies

PO1323

Whole-Exome Sequencing as a First-Line Diagnostic Tool in Bartter and Gitelman Syndromes

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Background: The clinical diagnosis of Bartter (BS) and Gitelman syndrome (GS) can be challenging, as they are rare and phenotypically overlapping. Thus, genetic testing represents the gold standard for the diagnosis. Next-generation sequencing is increasingly utilized in diabetics and research of inherited tubulopathies. Sequencing of gene panels achieved high diagnostic yield and new insights into the phenotype spectrum of these rare disorders. Whole-exome (WES) is not routinely performed for the molecular diagnosis of BS and GS. The aim of our study was to assess the diagnostic performance of WES in BS and GS, to establish genotype-phenotype correlations and to assess cost-effectiveness of this approach.

Methods: We performed WES in all consecutive patients referred for genetic testing with a clinical suspicion of BS or GS. Variant prioritization was carried out according to ACMG guidelines. Clinical data were collected retrospectively.

Results: We enrolled 50 patients (22 males) with a clinical diagnosis of BS or GS. All the patients showed hypokalemic metabolic alkalosis at onset. The median age at clinical diagnosis was 7 years (range 0-67). WES showed pathogenic variants in 41/50 patients (82%). A dedicated analytic pipeline allowed us to identify copy number variations (CNVs) in 7/41 patients with a confirmed genetic diagnosis. In details, WES allowed us to confirm the clinical diagnosis in 33/50 patients and to change it 8 additional patients (6 patients from BS to GS, 2 patients outside the BS/GS spectrum). Nephrocalcinosis was detected in 38% vs 8% of patients with a genetic diagnosis of BS and GS, respectively. Hypoparathyroidism was similarly distributed among BS and GS patients (45% vs. 68%). Finally, patients with GS showed a median age at onset higher than patients with BS, but some overlap did exist, making differential diagnosis challenging at single-patient level.

Conclusions: The results of our study demonstrate that WES ensures a high diagnostic yield in patients with a clinical diagnosis of BS or GS, especially if coupled with analysis of CNVs. This approach showed to be useful in dealing with the phenotypic heterogeneity typical of these rare disorders, improving differential diagnosis by detecting phenocopies also outside the BS/GS spectrum.

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PO1324
Examination of the Predicted Prevalence of Gitelman Syndrome by Ethnicity Based on Genome Databases
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Background: Gitelman syndrome is an autosomal recessive inherited salt-losing tubulopathy. It has a prevalence of around 1 in 40,000 people, and heterozygous carriers are estimated at approximately 1%, although the exact prevalence is unknown because most cases are thought to be asymptomatic or have nonspecific clinical findings. On the other hand, it has been reported that the non-specific symptoms can reduce the quality of life of patients, and in practice, we have often experienced cases where patients have suffered from these symptoms since childhood, but were not diagnosed and therefore not treated, and were diagnosed in adulthood. It could suggest that there are far more patients and carriers than expected.

Methods: We estimated the predicted prevalence of Gitelman syndrome based on multiple genome databases, HGVD and Jmorp for the Japanese population and gnomAD for other ethnicities, and included all 274 pathogenic missense or nonsense mutations registered in HGMD Professional. The frequencies of all these alleles were summed to calculate the total variant allele frequency in SLC12A3 which is the responsible gene for Gitelman syndrome. The carrier frequency and the disease prevalence were assumed to be twice and the square of the total allele frequency, respectively, according to the Hardy–Weinberg principle.

Results: In the Japanese population, the total carrier frequencies were 0.0048 (9.5%) and 0.0068 (8.7%) and the calculated prevalence was 0.00225 (2.1% in 1000 people) and 0.00188 (1.9 in 1000 people) in HGVD and Jmorp, respectively. Other ethnicities showed a prevalence varying from 0.000012 to 0.00083.

Conclusions: These findings indicate that the prevalence of Gitelman syndrome in the Japanese population is higher than expected and that some other ethnicities also have a higher prevalence than previously been considered.

PO1325
An Off-the-Shelf CRISPR Gene Therapy Approach in Human Kidney Organoids
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Background: Gene therapy offers many opportunities to treat kidney diseases. Targeted, off-the-shelf therapies are needed for both loss-of-function (e.g. nephronophthisis) and gain-of-function (e.g. Apol1) disease states. Kidney organoids are complex structures that resemble nephrons and can be used to develop gene therapy approaches. Commonly used gene transfer techniques, such as lentivirus and adenovirus, are size limited, transient, or introduce DNA non-specifically into the genome. While targeted CRISPR gene editing is routinely used in 2D cell cultures, it has not been challenging to use this powerful technique in intact organoids.

Methods: To achieve off-the-shelf gene transfer, organoids were transfected with Cas9 and gRNA ribonucleoprotein (RNP) complexes targeting the AATS1 safe harbor locus supplemented with knock-in cassettes encoding green fluorescent protein (GFP) or FLAG-tagged cystinosin (deficient in nephropathic cystinosis). Alternatively, to monitor gene knock-out, organoids expressing GFP from a genome. While targeted CRISPR gene editing is routinely used in 2D cell cultures, it has not been challenging to use this powerful technique in intact organoids.

Results: GFP and cystinosin knock-in events in organoids were detected using microscopy and PCR. Immunofluorescence analysis revealed knock-in in proximal tubule epithelial cells (LTL+). In knock-out experiments, live confocal microscopy indicated areas of GFP loss within kidney organoids treated with gRNA targeting GFP, but not with a scrambled guide. Mosaic patches of GFP knockout cells expanded over several days. Staining with nephron markers such as LTL and podocysin revealed knockout in both proximal tubule cells and podocytes. By next generation sequencing, the two-guide system produced larger deletions and was more efficient (20 % knockout), compared to single guide.

Conclusions: The strategy developed here is efficient for knocking in and knocking out genes in kidney epithelium. It uses commercially available reagents to perform CRISPR gene editing. sgRNA sequences or AATS1 knock-in templates can be customized to target or introduce any gene of interest at specific loci. This provides a platform for the development of off-the-shelf gene therapies for diverse kidney disease states.

Funding: NIDDK Support

PO1326
The Kidney Genome Atlas: A Resource to Understand APOL1 and Other Genetic Drivers of Adult Proteinuric Kidney Diseases
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Background: Chronic kidney disease (CKD) affects more than 30 million people in the US with African Americans being particularly at risk. There is an unmet need for pharmaceutical therapies that extend or, ideally, restore kidney function.

Methods: To guide genetically-driven drug development, we have established the Kidney Genome Atlas (KGA), which contains whole-genome sequences (>30x) from adult patients with Focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and other, idiopathic, proteinuric disorders as well as public and technically matched controls. By implementing a rigorous quality control procedure, following the gnomAD pipeline, we obtained a high-confidence dataset for downstream analyses. Three genetically inferred ancestries (EUR, AFR, AMR) were included in association testing comparing 1400 cases, including 169 individuals with APOL1 G1/G1, G2/G2 or G1/G2 high risk haplotypes (APOL1-HRH), with 1468 controls (including 485 APOL1-HRH individuals).

Results: Overall, our common variant cross-ancestry meta-analysis showed minimal impact on potential confounders, such as ancestry or sequencing center differences (lambda=1.03). Using summary statistics from our EUR analysis, we estimated a SNP heritability of 0.15 (SE = 0.028) in proteinuric diseases. Comparison to a recent CKD GWAS (Wuttke et al., 2019) indicated a weak positive genetic correlation (rg) of 0.097 (SE = 0.053). We identified the previously reported significant disease association of APOL1-HRH (p=2x10^-10) in our study. Recent in vitro data suggests amino acid in position 150 (rs2239785) is critical for the pathogenicity of APOL1-HRH (PO1986, ASN 2020) which we confirmed in our cohort of AFR ancestry individuals.

Conclusions: We have built a high-quality, multiethnic cohort that enables understanding of genetic drivers of polygenic proteinuric kidney disease. Future analysis including genetic modifiers of APOL1 may provide opportunities for novel therapies and patient stratification.

Funding: Commercial Support - Goldfinch Bio

PO1327
Effect of Apol1 Genotype on Kidney Failure and eGFR Decline in Patients with All-Cause CKD

Background: Apol1 risk variants G1 and G2 associate with an increased risk of kidney failure and a higher rate of eGFR loss. We assess the effect of Apol1 genotype in African American and Latino individuals with chronic kidney disease (CKD) in New York City.

Methods: Apol1 genotype determined by sequencing. CKD cases with high-risk Apol1 genotype (n= 242) were compared to CKD cases with a low-risk Apol1 genotype (n=885) and African ancestry per Admixture. Kaplan-Meier survival analyses assessed time to kidney failure followed by Adjusted Cox-proportional hazard model and competing risk regression against death both incorporating covariates. Linear mixed-effects modelling evaluated CKD-EPI eGFR_e decline rate using the same covariates.

Results: Cases with a high-risk Apol1 genotype reach kidney failure 10-15 years earlier than low-risk cases. G1/G1 reach kidney failure earliest, followed by G1/G2 and G2/G2 (Fig 1). These data are supported across multiple risk models (Table 1). Cases with a high-risk Apol1 genotype have a higher eGFR decline rate than low-risk cases with a similar trend per specific genotype (Fig 2). The addition of self-declared or genetically defined ancestry did not confer additional risk.

Conclusions: High-risk Apol1 genotypes increase the risk of kidney failure at an earlier age, likely due to a higher eGFR decline rate. G1/G1 genotypes appear most affected and G2/G2 least.

Funding: Government Support - Non-U.S.

Table 1. Modelling Results by Apol1 Genotype

<table>
<thead>
<tr>
<th>Apol1 Genotype</th>
<th>End-of-Life Change (eGFR_e)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1/G1</td>
<td>0.32 (-8.2, -0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1/G2</td>
<td>0.32 (-7.9, -0.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G2/G2</td>
<td>0.32 (-7.6, -0.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p < 0.05  **p < 0.001  ***p < 0.0001

Underline represents presenting author.
POI328

“APOL1-Plus Gene” Genotypes in Patients with CKD

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Background: Inheritance of homozygous or compound heterozygous APOL1 G1 G2 risk alleles is associated with an increased risk of chronic kidney disease (CKD) including focal segmental glomerulosclerosis (FSGS). The APOL1 high-risk genotype (HRG) is not completely penetrant; additional genetic and/or environmental factors are thought to be necessary for the development of CKD. While approximately 10% of individuals with CKD have causal variants when tested with exome-based next generation sequencing (NGS), few reports have examined co-occurrence of APOL1 HRG alongside these variants. Here we examine the co-occurrence of APOL1 HRG and additional genetic diagnoses ("APOL1-plus") using a broad NGS panel of >380 genes associated with isolated or syndromic CKD. Positive results had one pathogenic (P) or likely pathogenic (LP) variant in an autosomal dominant or X-linked gene, two P/LP variants in an autosomal recessive gene, or presence of two APOL1 risk alleles.

Results: Among 1691 cases with positive results, 25% (n=430) had positive findings in APOL1. Other positive findings included variants in PKD1/2 in 27% (456/1691) of cases, and in COL4A3/4/5 in 22% (379/1691) of cases. Among positive cases, 7% (119/1691) had 1 positive result, including both dual (n=115) and triple diagnoses (n=4). APOL1 HRG was present in 50% (59/119) of cases with multiple diagnoses, accounting for 3.5% of all positive cases and 14% of all APOL1 HRG cases. Among the APOL1-plus cases, second positive findings were observed in COL4A3/4/5 (29%; 17/59), TTR (29%; 17/59), and PKD1/2 (15%; 9/59).

Conclusions: Dual diagnoses comprised 7% of all positive genetic testing results, with APOL1 HRG present in half of these cases. Future studies are needed to understand how multiple genetic diagnoses, including those with APOL1 HRG, impact disease presentation and progression. Dual APOL1 and collagen IV-related diagnoses are of particular interest given the frequency of these glomerulopathies in the CKD population. Genetic testing via broad NGS panels can improve diagnosis and management of CKD and increased testing will contribute to an evolving understanding of genetic etiologies of CKD.

POI329

Uncovering Mechanisms of Risk-Variant APOL1-Modulated Inflammation Signaling in Macrophages

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Background: In the United States, Black Americans face a higher risk to develop CKD and progress to end stage kidney disease (ESKD) even after accounting for clinical and socioeconomic factors. Variants in the gene encoding for innate immunity factor Apolipoprotein L1 (APOL1) have been identified as risk factors for focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy (HIVAN) in individuals with recent African ancestry. However, the role of immune cells in APOL1 nephropathy is not well understood. In this study we seek to understand the effect of risk variant APOL1 on macrophage function and inflammation.

Methods: Isogenic induced pluripotent stem cell (iPSC) lines expressing the G0, G1, and G2 variants of APOL1 were generated through CRISPR/Cas9 gene editing. These iPSC lines were used to generate iPSC-derived macrophages (iPDSM). Pertussin and bone marrow-derived macrophages (BMMDMs) were collected from transgenic mice 4-18 weeks of age expressing G0, G1, and G2 variants of APOL1 in cultured iPDSM, peritoneal macrophages, and BMMDMs was induced with INFγ (5 ng/mL).

Results: We observed that risk-variant APOL1 expression results in higher TNF and IL1β gene expression by nine-fold and two-fold respectively, in G1 and G2 compared to G0 (P < 0.05). In APOL1 transgenic mouse peritoneal macrophages, oil red O staining revealed 2.83-fold increased neutral lipid accumulation (N = 3, P = 0.01) and 4.84-fold decreased efflorescence capacity measured with flow cytometry (N = 5, P = 0.05) in G1 and G2 mice as compared to G0. qRT-PCR analysis showed glycosylation genes to be increased in G1 iPDSM compared to G0. Additionally, G2 mouse BMMDS induced greater glycolytic rate compared to G0 both at baseline and under mitochondrial stress when APOL1 was induced with INFγ.

Conclusions: The findings in this study unveil some mechanisms by which risk-variant APOL1 modulates macrophage inflammatory phenotype and function, relevant to kidney disease progression.

Funding: Private Foundation Support

POI330

A Multivariate Analysis of Genome-Wide Association (GWAS) Data to Identify Genes Associated with CKD

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Background: Chronic kidney disease (CKD), a major public health burden, is characterised by a progressive loss of nephron function which leads to an impaired ability to filter the blood. Genome-wide association studies (GWASs) have identified single nucleotide polymorphisms (SNPs) and loci associated with the kidney function biomarkers estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) by mostly univariate-based analyses. However, gene-based multivariate-SNP and multivariate-biomarker relationships have typically not been considered so far in this context. The purpose of this study was to highlight the additional insights gained from the statistical power of a multivariate-based approach to identify potential risk factor genes for CKD.

Methods: We used a multivariate statistical approach, canonical correlation analysis (CCA), to identify single nucleotide polymorphisms (SNPs) that showed significant correlation with estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) taken jointly. For the significant SNPs and genes we identified, their functions, signalling pathways and cellular expression were investigated using gene set enrichment analyses.

Results: For each of three published GWAS summary statistics datasets of both European and Japanese ancestry groups, we identified sets of 159, 246 and 181 protein-coding genes, respectively, that contained significant SNPs. Using genome set statistical enrichment analyses, these genes showed significant enrichment for kidney development processes, signalling pathways and kidney cell gene expression signatures. In addition, between all three datasets, we identified four significant genes (CBLB, MACROD2, MECOM and SHROOM3) that overlapped. Between two datasets, we identified a further four significant SNPs that overlapped.

Conclusions: By using a multivariate statistical approach, we have identified both previously reported and additional genes that contained SNPs statistically associated with FKSD function. Overall, these findings provide new insights into SNPs and genes potentially involved in kidney function and CKD risk.

Funding: Government Support - Non-U.S.
PO1332
Genomic Disorders Are Associated with CKD Across the Life Span

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Background: Genomic Disorders (GDs), caused by pathogenic deletions and duplications (copy number variants, CNV) of large genomic regions, are a major source of genetic susceptibility for multiple developmental traits and are enriched in pediatric chronic kidney disease (CKD) patients. In the Chronic Kidney Disease in Children Study (CKiD) cohort 1, 4.5% participants carried a GD.

Methods: We extended our previous study in CKiD to cohort 2 and also examined the prevalence of GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency (CRI, N = 3375), Columbia University CKD (CU-CKD, N=1146) and Family Investigation of Nephropathy and Diabetes (FIND, N=1318) cohorts, comparing them to 30746 controls. CNV calls were based on SNP microarrays and whole exome sequencing and annotated for known GDs. We also performed a phenome-wide association analysis of GDs in the Electronic Medical Records and Genomics (eMERGE, N=11971) cohort.

Results: We found 9,248 (3.6%) CKD 2 pediatric participants with mild childhood carried a GD, replicating prior findings in pediatric CKD. We next identified GDs in 74,467 1(1.1%) adult CKD patients in the CRIC, CU-CKD and FIND cohorts, compared to 165,30,246 (0.5%) GDs in controls (OR=1.6, p=5x10^-4). Recurrent known GDs in adult CKD patients comprised pathogenic CNVs in 1q21.1, 16p11.2, 17q12 and 22q11.2 loci. The 17q12 GD (renal cyst and diabetes syndrome) was most frequent, detected in 1:252 CKD patients comprised pathogenic CNVs in 1q21.1, 16p11.2, 17q12 and 22q11.2 loci.

Conclusions: GDs are significantly enriched in children and adults with CKD. Undiagnosed GDs can provide a molecular explanation for renal disease in both adults and children and represent hidden genetic links between CKD and other traits such as poorer neurocognitive performance. Systematic detection of GDs can enable a precise genetic diagnosis and inform prognosis and treatment.

Funding: NIDDK Support, Other NIH Support - Geisinger Clinic

PO1333
Genome-Wide Association Study in Mice Maps Susceptibility to HIV-Associated Nephropathy to the Ssbp2 Locus

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Background: To gain insight into the pathogenesis of collapsing glomerulopathy, a rare form of focal segmental glomerulosclerosis that often arises in the setting of viral infections, we performed a genome wide association study (GWAS) among inbred mouse strains using a murine model of HIV-1 associated nephropathy (HIVAN).

Methods: F1 hybrids were generated between HIV-1 transgenic mice on the FVB/NJ background and 20 inbred laboratory strains. Histology, BUN, proteinuria and urinary NGAL were assessed in the F1 hybrids. A GWAS in 366 transgenic F1 hybrids generated from these 20 inbred strains was performed.

Results: Six strains (A/J, C3H/HeJ, DBA/1J, KK/HJ, WSF/EiJ, and LP/J) were highly sensitive to the Tg resulting in severe glomerulosclerosis, 9 strains (129S1/SvImJ, Balb/CJ, C57BL/6J, C57BL/6NJ, C57BL/10J, C57BL/1J, C3H/J, CAST/EiJ and NZB/BNJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 5 strains (CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HILF and FVB/NJ) had intermediate glomerulosclerosis. Analysis of histology, BUN and urinary NGAL demonstrated a marked phenotypic variation among the transgenic F1 hybrids, providing strong evidence for host genetic factors in the predisposition to nephropathy. A GWAS identified a genome-wide significant locus on Chr. 13 and multiple additional suggestive loci. Cross annotation of the Chr. 13 locus, including single cell transcriptional analysis of wild type and HIV-1 transgenic mice kidneys, nominated Ssbp2 as the likely culprit gene. Ssbp2 is highly expressed in podocytes, encodes a transcriptional cofactor present in LDB1 containing complexes, and interacts with LMX1B, a known FSGS gene that requires LDL1 for optimal transcriptional activity. Consistent with these data, older Sshp2 null mice spontaneously develop glomerulosclerosis, tubular casts, interstitial fibrosis and inflammation, similar to the HIVAN mouse model.

Conclusions: These findings demonstrate the utility of GWAS in mice to uncover host genetic factors for rare kidney traits and suggest Ssbp2 as susceptibility gene for HIVAN, potentially acting via the LDL1-1MX1B transcriptional network. Future studies will evaluate the role of Sshp2 in vitro and in Sshp2 null mice.

Funding: Other U.S. Government Support
Affected vs. Unaffected variant differences in one of the IgAN discordant twin pairs under analysis

**POI335**

**Primary AA Amyloidosis due to a chr11:18287683 T>C (hg19) Mutation in the SAA1 Promoter Linked to the Amyloidogenic SAA1.1 Haploype**

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**Background:** AA amyloidosis results from deposition of amyloid A (AA), a product of the proteolytic cleavage of serum amyloid A (SAA) proteins. Previously described AA amyloidosis has been due to increased production and deposition of serum amyloid A (SAA) proteins secondary to inflammatory conditions arising from infectious or metabolic causes. We describe for the first time a family with primary AA amyloidosis due to an isolated increase in production of AA protein.

**Methods:** A family was identified with autosomal dominant transmission of amyloidosis affecting 12 family members and associated with progressive chronic kidney disease (CKD) as well as other systemic manifestations of amyloidosis. Family members underwent measurement of serum SAA and whole exome sequencing with targeted sequencing. The luciferase reporter assay was used to determine promoter activity.

**Results:** Affected individuals developed proteinuria, CKD and systemic deposition of amyloid composed specifically of the SAA1.1 isoform. Affected individuals had a doubling of the SAA1 promoter activity and sustained elevation of serum SAA levels that segregated in an autosomal dominant pattern in 12 genetically affected and in none of 6 genetically unaffected relatives with a LOD score of >5. Genetic evaluation revealed a chr11:18287683 T>C (hg19) mutation in the SAA1 promoter linked to the amyloidogenic SAA1.1 haplotype that segregated completely with affected individuals. Tocilizumab had a beneficial effect when prescribed early.

**Conclusions:** A mutation in the SAA1 promoter linked to the amyloidogenic SAA1.1 haplotype led to a doubling of production of SAA1, leading to characteristic findings of amyloidosis. This is the first investigation to show that manifestations of AA amyloidosis in humans are due solely to SAA overexpression. Idiopathic forms represent a significant and increasing proportion (15-20%) of all diagnosed cases of AA amyloidosis. Genetic screening of the SAA1 promoter should be pursued in individuals with AA amyloidosis without an obvious cause of systemic inflammation, especially if there is a positive family history. Contact apley@wakehealth.edu for genetic evaluation of familial amyloidosis.

**POI336**

**Genetic Testing in Focal Segmental Glomerulosclerosis (FSGS): Tale of Three Stories**

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**Introduction:** Genetic testing in kidney disease has improved our understanding of various etiologies of glomerular diseases. FSGS is a histopathological diagnosis with diverse causes and patterns of inheritance. Genetic testing in FSGS has unlocked a treasure of pathogenic mutations that are either limited to the kidney or represent a broader extra-renal manifestation. Here we present 3 biopsy proven cases of FSGS with different genetic polymorphisms and varied presentations.

**Case Description:** Case 1: 29-year-old female with scoliosis, hearing loss, right optic nerve coloboma presented with 1.5 g/day of proteinuria and normal renal function when she was 16 years of age. Kidney biopsy revealed FSGS with 90% foot process effacement. 13 years later, her renal function worsened, with serum creatinine 1.4 mg/dl (baseline 0.9 mg/dl), and urine protein creatinine ratio of 4 g/l. Her mother had undergone a kidney transplant complicated by reflux nephropathy and genetic testing showed a truncating c.430>T in P.144* which can lead to FSGS, optic nerve coloboma and papilloneuritis syndrome. Case 2: 21-year-old male with biopsy proven FSGS when he was 8 years old mentioned that his maternal grandfather suffered from unknown renal disease requiring dialysis and died in his 40’s. Genetic testing revealed hemizygous, truncating p.W58* variant in the CLCN5 gene. Variants in CLCN5 gene can cause Dent’s Disease manifesting later in life as proteinuria, nephrocalcinosis, hypercalcuria and renal failure. In addition he had variant of unknown significance NPHS1 designated p.T233A, and APOL1G2 risk allele predisposing him to develop FSGS. Case 3: 21-year-old male born with genital ambiguity, perineal hypoplasia, 46 XY karyotype was noted to have 14 g of proteinuria, low albumin and hypertension. Kidney biopsy revealed FSGS, abnormal glomerular basement membrane. Genetic testing was positive for heterogeneous insertion of WT-1 and morphologically mosaic microdeletion variant of SMARCA1 p.R200H which are pathogenic variants that cause renal failure due to defective podocyte development and dysfunction respectively.

**Discussion:** Genetic analysis for FSGS has become an important diagnostic tool in nephrology. We currently have over 50 genes that are known to be involved in FSGS. Reporting of different genetic variants and their occurrence is crucial to yield insight into our current understanding of FSGS.

**POI337**

**Whole-Exome Sequencing Generates a Monogenic Cause of Disease in 26% of 335 Families with Steroid-Resistant Nephrotic Syndrome**

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**Background:** Steroid resistant nephrotic syndrome (SRNS) overwhelmingly progresses to end-stage renal disease. To date, more than 59 monogenic genes have been identified that cause SRNS. We previously detected causative mutations in 26% of whole exome sequencing (Warezek CJASN 13:53, 2018) and in 29.5% of patients with SRNS using targeted panel sequencing (Sadowski JASN 26:1279, 2015). However, whole exome sequencing (WES) has become more accessible, with the advantage of detecting not only monogenic causes of SRNS, but also novel candidate NS-causing genes.

**Methods:** We employed whole exome sequencing (WES) to detect monogenic causes of SRNS in a large international cohort of 335 families with SRNS presenting before the age of 25 years.

**Results:** Samples were recruited from April, 1998 to December, 2018 (21 years). WES was performed at the Yale Center of Mendelian Genomics. First, we examined the WES data for mutations in 59 known genes known to cause SRNS. In 87/335 families (26%), we identified mutations in 22 of the known genes. There were also 7 genes that were identified in phenotypes of SRNS e.g. COL4A3. In 58 families (17.3%), we have identified mutations in a potential novel candidate gene for SRNS. We found a 48.1% solve rate in individuals with high homozygosity by descent and 15.4% solve rate in non-homozygous individuals, recapitulating similar solve fractions to what has been previously published (Sadowski C.JASN 26:1279, 2015).

**Conclusions:** This study confirms that ~26% of families with NS in our cohort are due to monogenic causes, WES is a viable way to diagnose the underlying cause of NS in children and young adults, and to suggest novel monogenic candidate genes of NS.

**Funding:** Other NIH Support - S01DK76683-14.

**POI338**

**Discovery of Podocyte-Specific Interaction Partners of the Nephrotic Syndrome-Associated Protein NOS1AP**

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**Background:** Recessiv NOS1AP mutations are a novel Mendelian cause of nephrotic syndrome (NS) in humans and mice (Majmundar Sci Adv 2021). The NS patient mutation p.C143Y destabilizes the predicted structure of the NOS1AP phosphotyrosine-binding domain, impairs NOS1AP-dependent actin remodeling in immortalized podocytes, and causes abnormal kidney organoid glomerulogenesis. Here, we aimed to discover podocyte-specific NOS1AP interaction partners, which may mediate NOS1AP functions in the podocyte and whose binding is abrogated by the patient mutation p.C143Y.

**Methods:** Protein interaction data from candidate immunoprecipitation, mass spectrometry, and yeast two-hybrid studies were queried from the literature and public databases (Oncomine NAR 2014; Oncoarray NAR 2019; Searlelab MX 2019). Gene expression was queried from kidney single cell mRNA sequencing (scRNAseq) datasets (Karaiskos JASN 2018; Menon Development 2018; Wang Cell Rep 2018; Wu JASN 2018). Protein interactions were validated by co-immunoprecipitation studies using patient and controls A constructs.

**Results:** 85 putative NOS1AP-interacting proteins were identified from candidate interaction and proteomics studies. Six interacting proteins (of 85) demonstrated co-expression with NOS1AP in podocyte clusters from at least three out of four kidney scRNAseq datasets (% cell expression z-score >1). Four of six candidates (FYN, GSN, SNTA1, HSPA12A) were cloned into expression vectors for interaction studies. SNTA1 and HSPA12A exhibited bi-directional co-immunoprecipitation with wildtype NOS1AP upon co-overexpression in a podocyte cell line. Co-immunoprecipitation was, similarly, observed with the NS patient mutant NOS1AP.

**Conclusions:** Our results suggest NOS1AP is co-expressed with and can physically interact with SNTA1 and HSPA12A in podocytes. These proteins may mediate NOS1AP functions in podocyte biology.

**Funding:** Other NIH Support - NIH Institutional K12 Child Health Research Center Career Development Award (5K12HD052896-13), Private Foundation Support.
Synuclein Alpha Accumulation Drives Lysosomal Dysfunction in Fabry Podocytopathy

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Background: Anderson-Fabry disease is an X-linked lysosomal disorder characterized by a multisystemic glycolipidosis, characterized by abnormal lysosomal glycosphingolipid accumulation due to reduced alpha-galactosidase activity (GLA). Podocyte injury is a major renal manifestation of Fabry disease. Recently, our data indicated Gb3 depletion to be insufficient in repairing podocyte damage seen in an in vitro model for Fabry disease. This project, therefore, focuses on the potential GL3 independent mechanisms in Fabry podocytopathy.

Methods: We employed CRISPR/Cas9 to generate GLA knock out lines of immortalized human podocytes in vitro. These cells were investigated by (ultra-) structural, transcriptome and proteome as well as functional analyses in the presence and absence of enzyme replacement therapy (ERT). The acquired data sets were integrated through network analysis and connectivity mapping. These data were complimented by the investigation of human biopsies taken sequentially before and after a period of ERT.

Results: We detected that enzyme replacement therapy (ERT) and Gb3 reduction failed to reduce Gb3 accumulation in patient biopsies. GLA knock out podocytes depicted high Gb3 levels that were fully reversed upon enzyme replacement. Still, lysosomal dysfunction was significantly but not completely reversible with enzyme substitution. Proteomics suggested alpha-synuclein (SNCA) accumulation as a potential driver for podocyte dysfunction. Transcription-based connectivity mapping revealed a potential anti-SNCA therapeutic effect of beta-adrenoceptor agonists. Indeed, genetic and pharmacological inhibition of this protein significantly improved lysosomal structure and function in Fabry podocytes beyond the effects of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Stable Genetic Deletion of Gapvd1 in Drosophila Results in a Nephrocyte-Restricted Phenotype

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Background: Mutations in the gene GAPVD1 cause nephrotic syndrome in humans. GAPVD1 interacts with RAB5 and but the subcellular localization of GAPVD1 was unknown. Silencing of Gapvd1 in the podocyte-like Drosophila nephrocytes by RNA-interference resulted in mislocalization of fly nephrin.

Methods: We generated conditional knockdowns and a stable genetic deletion of Drosophila Gapvd1 by CRISPR/Cas9 and used microinjection-mediated end joiing to introduce a genomic HA-tag into the Gapvd1 c-termius. We performed a functional analysis of the novel fly models.

Results: We generated twin frameshift mutations at the second and third exons of the Drosophila Gapvd1 gene. Animals carrying these mutation were homozygous viable without any overt phenotype. However, the podocyte-like nephrocytes revealed a severely altered slit diaphragm morphology with mislocalization of fly nephrin and the orthologue of NEPH1 and partial loss of both proteins from the surface. This phenotype was similar but considerably stronger than the phenotype observed by RNA-mediated silencing. This suggests that the homozygous frameshift mutations result in a null allele. The phenotype was further confirmed by conditional CRISPR/Cas-mediated silencing using two different gRNAs. Deletion of Gapvd1 in the Drosophila model thus results in a phenotype that manifests exclusively in disturbed slit diaphragm formations. This recapitulates the nephrocyte-restricted phenotype.

Conclusions: We established suitable new Drosophila models to study the function of Gapvd1 in nephrocytes as an invertebrate podocyte model.

Pathogenicity Assessment of Non-Glycine Missense Variants in COL4A5 Collagenous Domain

Yuya Aoto,1 Tomoko Horinouchi,1 Tomohiko Yamamura,1,3 Chika Nagano,1 Atsushi Kondo,1 Sadayuki Nagai,1 Nana Sakakibara,1 Kazumoto Iijima,2 Kandai Nozu,3 Kobe Daigaku, Kobe, Japan; 2Hyogo Kenritsu Kodomoto Byoin, Kobe, Japan; 3Manchester Metropolitan University, Manchester, United Kingdom.

Background: COL4A5, which encodes type IV collagen α5 chain, is a causative gene of X-linked Alport Syndrome (XLAS). In triple-helical domain on collagen protein the phenotype observed in humans was limited to nephrotic syndrome, supporting the use of Drosophila model for this genetic disease. To study the subcellular localization of Drosophila Gapvd1, we introduced an HA-tag into the c-termius of the Gapvd1 locus. Immunofluorescence of nephrocytes derived from the knock-in lines showed that overexpression of ΔN117 led to mislocalization of fly nephrin. The glomerular localization of fly nephrin was altered in the Drosophila Gapvd1 gene. Animals carrying these mutantion were homozygous viable without any overt phenotype. However, analysis of the podocyte-like nephrocytes of these flies revealed a potential anti-SNCA therapeutic effect of beta-adrenoceptor agonists. Indeed, genetic and pharmacological inhibition of this protein significantly improved lysosomal structure and function in Fabry podocytes beyond the effects of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.

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Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.
A Human Missense Integrin-Linked Kinase Variant Negatively Regulates Murine Renal Branching Morphogenesis via mTOR Signaling

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Background: Branching morphogenesis is critical to kidney development and the pathogenesis of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Identification of gene variants via genomic sequencing aims to elucidate molecular mechanisms underlying CAKUT. The pathogenic contributions of such variants are largely unknown; functional analyses are required to identify pathogenic mechanisms. Here, we identify pathogenic effects of a CAKUT-associated human missense variant of Integrin-Linked Kinase (ILK), a key regulator of renal branching morphogenesis, on ureteric branching.

Methods: Targeted gene panel sequencing was performed to identify gene variants. ILK-T173I function was investigated in mouse inner medullary collecting duct (mIMCD3) cells and mouse embryonic kidney explants transduced with lentivirus expressing ILK-T173I. Gene expression was analyzed by RNA microarray and validated by qPCR and Western analysis. Mutant mice with a ILK c.518C>T point mutation were generated using CRISPR/Cas9. Morphological effects of ILK-T173I on ureteric branching were visualized using Hoxb7-driven fluorescent marker (MyrVenus) and quantitated by counts of ureteric bud tips and nephrons.

Results: An ILK missense variant, ILK-T173I, was identified in a CAKUT patient and her mother by targeted gene panel sequencing and verified by Sanger sequencing. mIMCD3 cells expressing ILK-T173I demonstrated dysregulated expression of AKT/mTOR target mRNAs, identified by RNA microarray and qPCR, and elevated levels of phospho-p70S6Kinase, a mTOR target (n=3, P<0.003). Overexpression of ILK-T173I in embryonic kidney explants increased phospho-p70S6Kinase expression (n=3, P=0.03) and decreased ureteric tip number by 50% (n=15, P=0.003), both of which were rescued by treatment with Rapamycin, an mTOR inhibitor (n=4, P=0.04). Knock-in mice in which ILK-T173I replaces the ILK-WT allele were characterized by low nephron number (n=6, P=0.04) and decreased ureteric branching (n=5, P=0.006), and increased expression of phospho-p70S6Kinase (n=3, P=0.014). Treatment of mutant cultured embryonic kidney explants with Rapamycin rescued ureteric branching to levels observed in ILK-WT mice.

Conclusions: Human ILK-T173I variant decreases branching morphogenesis in an mTOR-dependent manner. Increased mTOR signaling disrupts mouse kidney development.

Funding: Government Support - Non-U.S.
Excess Burden of Rare Coding Variants in Mutation Intolerant Genes in Patients with Kidney Malformations
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Background: Renal hypoplasiasia (RHD) is one of the most common cause of pediatric kidney failure. Although multiple causative genes have been identified, they only account for 10-15% of cases. The contribution of rare variants has not been systematically examined.

Methods: To evaluate the contribution of rare variants to RHD, we analyzed exome sequencing (ES) data in 1,265 unrelated RHD cases and 13,303 unrelated controls. We used gene-level burden analysis, comparing the proportion of cases and controls carrying rare variants per gene across 20 statistical models.

Results: We observed a 1.63-fold case enrichment for rare variants (p=1.5x10^{-10}) in known genes associated with dominant forms of kidney diseases (165 cases versus 1,075 controls in 172 known genes), including PAX2 (7.6x10^{-10}) and HNF1B (5.6x10^{-10}). All other known genes did not reach statistical significance (p-value<10^{-10}). Applying a similar approach, we observed a 1.35-fold case enrichment for rare missense variants (p=5.8x10^{-10}) in genes constrained against missenses (misZ >3.09) and a 1.59-fold enrichment for rare protein truncating variants (PTV; p=2.4x10^{-10}) in genes constrained against PTV (pLift<0.9 and oe lof upper<0.35). We particularly identified a 2.38-fold enrichment for PTV in 421 genes constrained against PTV, expressed in the mouse developing kidney (E15.5), and not known to be associated with human kidney disease (p=1.4x10^{-6}).

Conclusions: We detected a significant excess of rare variants in mutation intolerant genes that are also expressed during early kidney development, suggesting the existence of many yet-to-be-identified causal genes. However, owing to the high genetic heterogeneity of RHD, larger-scale investigations will be required to establish causality for individual genes.

Funding: NIDDK Support

Reverse Phenytoin Facilitates Disease Allele Calling in Whole-Exome Sequencing of Patients with Congenital Anomalies of Kidney and Urinary Tract (CAKUT)
Steve Seltszam, Chunyan Wang, Bixia Zheng, Dervla M. Connaughton, Chen-Han W. Wu, Sophia Schneider, Luca M. Schierbaum, Shleree Shril, Friedhelm Hildebrandt, Boston Children’s Hospital, Boston, MA.

Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the leading cause of chronic kidney disease in children and young adults. To date, 174 genes are known to cause isolated or syndromic monogenic RHD. However, incomplete penetrance and broad phenotypic heterogeneity can impair disease allele identification, particularly in syndromic CAKUT. We hypothesized that the yield of a genetic diagnosis can be increased by combining whole exome sequencing (WES) with reverse phenotyping, in which the contributing physician is asked to examine a patient for signs/symptoms that may occur in the suspected clinical syndrome that results from the genetic variant detected by WES.

Methods: We conducted WES in an international cohort of 823 individuals with CAKUT from 732 unrelated families and evaluated WES data for variants in the 174 genes in which variants are known to cause isolated or syndromic CAKUT. In cases in whom the likely causative genotype suggested a syndromic phenotype that was not reported at enrollment, we conducted reverse phenotyping.

Results: In 84/732 (11.5%) families, we detected a likely causative variant consistent with an isolated or syndromic CAKUT phenotype. In 19 of the 84 families (22.6%) with detection of a likely CAKUT-causing variant, reverse phenotyping yielded syndromic findings, thereby strengthening the genotype-phenotype correlation.

Conclusions: We conclude that employing reverse phenotyping in the evaluation of (facultative) syndromic CAKUT genes by WES provides an important tool to establish a more valid and specific diagnosis mitigating the broad phenotypic and genotypic heterogeneity of CAKUT.

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Ultrabright Plasmonic-Fluor Nanolabel-Enabled Detection of a Urinary Biomarker in ADTKD

**Background:** Tubulointerstitial Kidney Disease

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**PO1351**

**Relationship:** Non-U.S.

**Funding:**

**Conclusions:** We have utilized CRISPR/Cas9-generated mice with mutant UMOD and by harnessing a newly invented ultrabright fluorescence nanoconstruct, termed “plasmonic fluor (PF)” (Nat Biomed Eng 2020).

**Results:** In the murine model and patients with ADTKD-UMOD, we find that immunoglobulin heavy chain-binding protein (BiP), an ER chaperone, was exclusively upregulated by mutant UMOD in TAL and easily detected by Western blot in the urine at an early stage of disease. However, even the most sensitive ELISA failed to detect urinary BiP in affected individuals. We therefore developed the ultra-sensitive, plasmon-enhanced fluorescence-linked immunosorbent assay (p-FLISA) to detect the urinary biomarker in ADTKD patients by harnessing a newly invented ultrabright fluorescent nanoconstruct, termed “plasmonic fluor (PF)” (Nat Biomed Eng 2020).

**Methods:** We have utilized CRISPR/Cas9-generated mice with Umod-C147W mutation, analogous to human UMOD-C148W mutation, and ADTKD-UMOD patients to discover a novel endoplasmic reticulum (ER) stress biomarker. In addition, we have developed an ultrasmall, plasmonic-enhanced fluorescence-linked immunosorbent assay (p-FLISA) to detect the urinary biomarker in ADTKD patients by harnessing a newly invented ultrabright fluorescent nanoconstruct, termed “plasmonic fluor (PF)” (Nat Biomed Eng 2020).

**Conclusions:** By developing the ultra-sensitive p-FLISA, we have identified secreted BiP as a novel urinary ER stress biomarker with potential utility in risk stratification, prediction of disease progression and guidance of ER-targeted therapies in ADTKD.

**Funding:** NIDDK Support, Other U.S. Government Support

**PO1352**

Genetic Analysis of a Brazilian Nephropathic Cystinosis Cohort Reveals Novel CTNS Variants Mostly of Non-European Origin

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**Background:** Nephropathic Cystinosis (NC) is a severe autosomal recessive disease caused by intralysosomal cystine deposition. Most CTNS variants have been described in Europe and North America, where a specific 57kb deletion (del) is the most frequent one. In this study, we sought to characterize the CTNS variants and their genetic ancestry profiles in a NC Brazilian cohort, an admixed population.

**Methods:** 61 NC patients were studied, both sexes, ≥21 years old, followed at the University of Sao Paulo Medical Center. Mutation analysis was performed by gel electrophoresis and/or MLPA to assess the 57kb del, and NGS targeted sequencing. To characterize the genetic ancestry profiles, 48 patients were genotyped with a high-density SNP array. The average genomic ancestry was inferred using ADMIXTURE and the ancestry of the CTNS gene region using RFMix.

**Results:** Two disease-causing variants were identified in 58/61 patients, followed by segregation analysis whenever possible. The detected variants included 9 previously reported and 7 novel ones. Previously reported variants were observed in European genomic segments, except the African ancestry-linked variant c.62-2A>G. Among the novel variants, 4 are in genomic segments of African origin (del exons 2.4, c.227delT, c.557delC, c.412del-P.w133R and c.457T>p.K153X), 1 in Native American (c.16-19del-P.L66S), 1 in an European-ancestry segment (c.262-*26del6insCGGCAG), and 1 could not be determined (c.158delC-P.w535fs). The highest allele frequencies were 57kb del (55.7%), c.382T (14.0%), c.16-19del (7.4%) and c.611-613del (5.7%). Analyses of LD decay support that 57kb del, c.382T and c.611-613del originated in Europe at least 1,750 years ago (250-3,750 years ago) and 275 years ago (75-1,200 years ago), respectively, and suggest that c.16-19del likely originated in America 15,025 years ago (5,775-41,000). A new invention, c.62-2A>G, most likely originated in Europe at least 1,750 years ago.

**Conclusions:** We have utilized CRISPR/Cas9-generated mice with mutant CTNS and by harnessing a newly invented ultrabright fluorescent nanoconstruct, termed “plasmonic fluor (PF)” (Nat Biomed Eng 2020).

**Funding:** NIDDK Support, Other U.S. Government Support

**PO1353**

Adult Zebrfish as a Model to Study Renal and Extrarenal Manifestations of Cystinosis

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**Background:** Cystinosis is a rare autosomal recessive disease caused by mutations in the CTNS gene, which encodes for the cystine transporter cystinosin leading to lysosomal cystine accumulation in all cells of the body, with kidneys being the first affected organs. The current treatment with cysteamine decreases the lysosomal cystine accumulation, but does not reverse the renal Fanconi syndrome, glomerular injury or loss of renal function. We have developed a zebrfish larval model having truncating mutation in ctns, which recapitulates the kidney phenotype of cystinosis. However, long-term disease consequences in adult zebrfish have not been studied so far. In this study, we characterized the adult zebrfish model to evaluate the late effects of cystinosis on kidney and extra renal organs.

**Methods:** Cystinosis (ctns<sup>-/-</sup>) zebrfish of 18 months and wild type (WT) zebrfish were studied. Histologic examinations of kidneys and extra-renal organs were performed. Cleaved caspase-3 staining was used to evaluate apoptosis in the kidney. Cystine accumulation was evaluated via liquid chromatography-mass spectrometry and toluidine blue staining. For the fertility studies, the number of total eggs and fertile eggs produced by breeding female and male ctns<sup>-/-</sup> zebrfish compared to WT zebrfish was evaluated.

**Results:** ctns<sup>-/-</sup> zebrfish show increased cystine level, glomerular hypertrophy and proximal tubular accumulation of hyaline-like eosinophilic droplets and vacuolated cytoplasm. Moreover, the cystinotic zebrfish exhibit increased cleaved caspase-3, indicating enhanced apoptosis in the proximal tubules. In addition, instead of the typical striped pattern, ctns<sup>-/-</sup> zebrfish present an altered melanin skin pigmentation, resulting in spotted skin. Lastly, male ctns<sup>-/-</sup> zebrfish show spermatogenic cysts enriched in spermatozoa, while female display increased percentage of unfertilized eggs.

**Conclusions:** The adult ctns<sup>-/-</sup> zebrfish model reproduces several phenotypes of cystinosis, such as altered glomerular and proximal tubular morphology, whole body cystine accumulation, impaired skin pigmentation and decreased fertility. Therefore, this model may be useful for studying long-term effects of cystinosis and for the development of new therapeutic strategies for correcting cystinosis, which is - up to now - incurable.
Vascularized Kidney Organoids on Chip for Efficacy and Toxicity Testing of Somatic Genome Editing

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Background: Somatic genome editing has therapeutic potential to cure inborn diseases. Clinical translation requires safety and efficacy analyses. DNA editing may be widely discrepant across species due to genomic differences, necessitating human tissue-based platforms. AAV-based delivery of DNA editing elements is under clinical investigation. If delivered systemically, the kidney may be particularly susceptible to genome editing owing to high blood flow. Kidney organoids have been generated from human stem cells through the co-induction of nephron, stromal, and endothelial progenitor cells that mature to form multipolar organoids. We matrarchitectured and organ-on-chip technologies to facilitate the maturation of nephron epithelia and the development of perfusable vascular networks to simulate systemic delivery of genome editing elements.

Methods: Using human reconstituted growth factors and defined small molecules, kidney organoids were generated and differentiated into the kidney organoids. We engineered epithelia from proximal & distal tubules and podocytes of kidney organoids by single cellular transcriptomics. Biomarker analysis demonstrated a statistically significant increase in tubular injury markers, KIM-1 and MCP-1, in epithelia after infection with AAV2/2 as compared to other AAVs. Following treatment with AAV6-mCherry-GFP, the majority of LTU- and CDH1- tubular epithelia were GFP+, while PODXL+ podocytes were infected. The optimal AAV serotype, MOI, and duration of infection under static conditions were applied to vascularized kidney organoids. Initial on-chip testing supports enhanced infectivity by single-cell monitoring and whole-mount immunostaining, including AAV infection in GFP PODXL+ podocytes.

Conclusions: We propose vascularized kidney organoids may simulate the systemic delivery of AAVs across kidney compartments, as a pre-clinical testing platform of the efficacy and safety of somatic cell genome editing.

Funding: Other NIH Support - U01: SCGIE Consortium

Genotype and Phenotype Analysis in Patients with X-Linked Hypophosphatemia

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Background: X-linked hypophosphatemia (XLH) is the most frequent form of hypophosphatemic rickets and is caused by mutations in the PHExE gene. We analyzed genotype-phenotype correlations in XLH patients with proven PHExE mutations.

Methods: PHExE mutations were detected in 57 out of 81 patients who clinically presented with hypophosphatemic rickets. The patients were grouped into non-truncating (n = 11) and truncating (n = 46) mutation groups; their initial presentation as well as long-term clinical findings were evaluated according to these groups.

Results: Initial findings, including presenting symptoms, onset age, height standard deviation scores (SDs), and laboratory tests, including serum phosphate level and tubular resorption of phosphate, were not significantly different between the two groups (onset age: non-truncating mutation group, 2.0 years, truncating mutation group, 2.1 years; height SD: non-truncating mutation group, -1.9, truncating mutation group, -1.8; serum phosphate: non-truncating mutation group, 2.5 mg/dL, truncating mutation group, 2.3 mg/dL). However, at their last follow-up, the serum phosphate level was significantly lower in patients with truncating mutations (non-truncating mutation group: 3.2 mg/dL, truncating mutation group: 2.3 mg/dL, P = 0.003). Additionally, 62.5% of patients with truncating mutations developed nephrocalcinosis within their first follow-up, while none of the patients with non-truncating mutations developed nephrocalcinosis (P = 0.008). Orthopedic surgery due to bony deformations was performed significantly more often in patients with truncating mutations (52.3% vs 10.0%, P = 0.008).

Conclusions: Although considerable inconsistency exists regarding the correlation of truncating mutations and their disease phenotype in several other studies, we cautiously suggest that there would be genotype-phenotype correlation in some aspects of disease manifestation after long-term follow-up. This information can be used when consulting patients with confirmed XLH regarding their disease progression.

Childhood-Onset Nephrocalcinosis in Twins Caused By Biallelic Mutations in CYP24A1 Gene: A Long Journey to a Genetic Diagnosis

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Introduction: 24-hydroxylase deficiency is a rare autosomal recessive disorder caused by mutations in CYP24A1 gene, characterized by hypercalcemia, hyperparathyroidism and nephrolithiasis. Establishing a genetic diagnosis, while important to guide management and family counseling, can be challenging. We hereby report a case of twins with childhood-onset nephrocalcinosis and chronic hypercalcemia caused by biallelic mutations of CYP24A1, which took years to be diagnosed.

Case Description: A 26-year-old female presented for preconception evaluation for a history of childhood-onset nephrocalcinosis and chronic hypercalcemia. Patient reported similar history in identical twin sister. They had exome sequencing (ES) eight years ago after negative genes panel test which revealed a heterozygous variant of unknown significance (c.1186C>T) in CYP24A1. A reanalysis of ES was performed four years ago which demonstrated no changes. Work up revealed hypercalcemia, low 25(OH) vitamin D, elevated 1,25(OH) vitamin D and 24,25(OH) vitamin D, and suppressed PTH(fig.1). Ratio of 25(OH)D to 24,25(OH)D, a new biochemical test for 24-hydroxylase deficiency, suggested biallelic mutations in CYP24A1 gene. ES reanalysis at this time reclassified the c.1186C>T variant as pathogenic and disclosed a novel intronic variant (c.544-1G>A) which was predicted to cause splicing pattern change with multiple silico algorithms. Parental tests confirmed these two variants were in trans configuration consistent with autosomal recessive inheritance pattern. A thorough counselling included low recurrence risk for her children while high risk for her to develop severe hypercalcemia during pregnancy. She has been closely monitored with low calcium and vitamin D diet, sun avoidance and adequate hydration during current pregnancy with no complications to date.

Discussion: CYP24A1 gene related hypercalcemia is rare and challenging to diagnose even with ES. This case suggests the benefits of ES regular reanalysis for clinically suspected patients with inconclusive genetic findings. The novel intronic mutation identified in this case broadens the genetics spectrum of 24-hydroxylase deficiency.
POI1359

TRPV4 Calcium Channel Activity Is Increased by With-No-Lysine
Kinase 1 in the Collecting Duct Cells

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Background: Kidneys play a central role in regulation of potassium homeostasis and maintaining plasma K+ levels within a narrow physiological range. Dietary K+ load increases circulating levels of the mineralocorticoid aldosterone leading to kalisuresis via stimulation calcium-activated large conductive maxi-K+ (BK) channel dependent K+ secretion in the collecting duct cells. WN1K and WN4K (With-no-lysine) kinases, have been recognized to regulate K+ balance, in part, by orchestrating BK-dependent K+ secretion in the ASDN (aldosterone sensitive renal nephron). Ca2+-permeable TRPV4 channel is essential for BK activation in the distal nephron, as we have recently demonstrated. Also of note, high K+ diet increases TRPV4 activity and expression largely in an aldosterone-dependent manner.

Methods: Patch-Clamp; [Ca2+]i imaging; Western blotting; Real-Time PCR.

Results: In the current study, we aimed to test whether WN1K/4 contribute to regulation of TRPV4 by aldosterone. First we investigated if TRPV4 is expressed in the kidney. The expression of TRPV4 was localized to the collecting duct cells. In WT mice, the expression of TRPV4 is upregulated under dietary potassium deficient conditions. However, in aldosterone dependent conditions, the expression of TRPV4 is downregulated.

Conclusions: Overall, we show that TRPV4 is essential in controlling aldosterone in collecting duct cells. We propose that the syncretism mechanism is likely contributing to regulation of urinary K+ levels to maintain systemic homeostasis.

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

POI1360

Cyclin M2 (CNNM2) Is Essential for Development and Systemic Magnesium Homeostasis

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Background: Patients with mutations in the Cyclin M2 (CNNM2) gene display hypomagnesemia and intellectual disability. CNNM2 is highly expressed in the distal convoluted tubule, where it is involved in renal magnesium (Mg2+) reabsorption. However, the complete phenotypical spectrum of the CNNM2-related disorder remains unknown. We characterized a large patient cohort with novel CNNM2 variants and used transgenic mouse models to investigate the role of CNNM2 in Mg2+ homeostasis.

Methods: The identified CNNM2 variants were found in a cohort of hypomagnesemic patients and characterized using [35S]Mg2+ transport assays in HEK293 cells. In addition, CNNM2-deficient mice were developed using CRISPR-Cas9 technology and exposed to deficient or saturated Mg2+ diets for two weeks. Using metabolic cages, the 24-hour urinary and faecal Mg excretion in WT and Cnnm2-/-, Cnnm2+/+ mice was determined.

Results: Eleven patients were identified with novel dominant variants in CNNM2. Using [35S]Mg2+ transport assays in HEK293 cells, seven variants showed decreased [35S]Mg2+ transport compared to wild type. These pathogenic mutations resulted in decreased membrane expression of CNNM2. The phenotype of these patients was compared with those previously published. Patients with pathogenic CNNM2 mutations had a more severe phenotype characterized by renal magnesium wasting, growth retardation, and neurological symptoms.

Conclusions: Overall, we show that CNNM2 is essential for normal development and Mg2+ homeostasis, although the clinical spectrum varies. Our mouse study suggests a putative role of CNNM2 in the intestine, which could have implications for the treatment of patients suffering from CNNM2 mutations.

Funding: Government Support - Non-U.S.
Infantile Hypercalcemia Associated with a Novel Homozygous Mutation in SLC34A1 Gene Encoding Sodium-Dependent Phosphate Transporter 2A
Mohamed Hassanen, Jordana Yahr, Mary-Beth Roberts, Xiangling Wang. Cleveland Clinic, Cleveland, OH.

Introduction: Early-onset and familial hypercalcemia often suggest a genetic etiology which is rare. Infantile hypercalcemia (IH) is a rare, autosomal recessive disorder that occurs due to mutations in the SLC34A1 gene which encodes a sodium-dependent phosphate transporter 2A(NaPi-IIA) responsible for phosphate reabsorption in the kidney. We report an adult case who carried a clinical diagnosis of familial hypocalcicaturic hypercalcemia (FH) since infancy, which is usually a benign condition characterized by autosomal dominant inheritance caused by mutations in calcium-sensing receptor (CASR) gene, while recently uncovered as IH related to a novel homozygous mutation in the SLC34A1 gene.

Case Description: A 36-year-old Finnish male with a diagnosis of FHH presented to the genetics nephrology clinic for consultation regarding the recurrence risk for his children. He was diagnosed with FHH during infancy in Finland and has been treated with a low calcium diet. Family history was notable for a clinical diagnosis of FHH in his older sister. Physical exam was unremarkable. Labs showed mild hypophosphatemia and decreased glomerular filtration rate (69 mL/min/1.73m2), with normal serum ionized calcium and intact parathyroid hormone. Twenty-four hour urine analysis revealed hypercalciuria 363 mg/d (normal <250), hypernatremia 155 mmol/d (normal 50 – 150) and hypoproteinaemia 420 mg/d (normal >450). Kidney ultrasound showed bilateral medullary nephrocalcinosis. Genetic testing identified a novel homozygous variant in SLC34A1 gene (c.1483C>T) and was negative in his older sister. Physical exam was unremarkable. Labs showed mild hypophosphatemia and decreased glomerular filtration rate (69 mL/min/1.73m2), with normal serum ionized calcium and intact parathyroid hormone. Twenty-four hour urine analysis revealed hypercalciuria 363 mg/d (normal <250), hypernatremia 155 mmol/d (normal 50 – 150) and hypoproteinaemia 420 mg/d (normal >450). Kidney ultrasound showed bilateral medullary nephrocalcinosis. Genetic testing identified a novel homozygous variant in SLC34A1 gene (c.1483C>T) and was negative in CASR gene family. Family genetic studies revealed his affected sister is also homozygous for the same variant while his unaffected sister is only a carrier. With the new diagnosis, he was started on potassium citrate and chlorthalidone, and was reassured with the low recurrence risk for his children.

Discussion: Mutations in the SLC34A1 gene lead to altered NaPi-IIA expression and reduced phosphate reabsorption, leading to hypophosphatemia. Secondary vitamin D activation leads to hypercalcemia, hypercalciuria, and nephrocalcinosis. We identified a novel mutation in the SLC34A1 gene which broadens the genetic spectrum of IH. This case highlights the importance of early genetic testing for suspected hereditary hypercalcemia that may help improve its diagnosis and treatment.

Characteristics and Genetic Defects of Systemic Lupus Erythematosus-Associated Thrombotic Microangiopathy
Cui Queuan, Peking Union Medical College Hospital, Dongcheng-qu, China.

Background: Thrombotic microangiopathy (TMA) is a life-threatening complication of systemic lupus erythematosus (SLE). However, the etiology of a considerable number of patients is still unclear and the best treatment is unknown. Sporadic reports suggest that the activation of complement pathway may play a role in SLE-TMA.

Methods: We prospectively enrolled 40 SLE-TMA patients in Peking Union Medical College Hospital, 14 patients with lupus nephritis (LN) and 38 patients with other types of TMA. The clinical data were collected. Peripheral blood concentrations of CFH, cCFB, soluble C5b-9, relative activity of complement pathway, ICAM1, VCAM1 and E-Selectin were measured by ELISA in SLE-TMA patients and control groups. Whole exome sequencing (WES) was performed to analyze the genetic variants in SLE-TMA patients.

Results: SLE-TMA mediated by ADAMTS13 inhibitors had severe nervous system involvement, but less kidney involvement and good response to plasma exchange. Among SLE-TMA with unknown etiology, patients with TMA confined to kidney had lighter hematological manifestations and lower serum creatinine level than those in SLE-aHUS patients with MAHA (p = 0.016). There was no significant difference in genetic susceptibility among SLE-TMA with unknown etiology, patients with TMA confined to kidney had lighter hematological manifestations and lower serum creatinine level than SLE-aHUS patients with MAHA (p = 0.016). There was no significant difference in genetic susceptibility among SLE-aHUS patients. Peripheral blood concentrations of CFH, cCFB, soluble C5b-9, relative activity of complement pathway, ICAM1, VCAM1 and E-Selectin were measured by ELISA in SLE-TMA patients and control groups. Whole exome sequencing (WES) was performed to analyze the genetic variants in SLE-TMA patients.

Conclusions: SLE-TMA with unknown etiology can be divided into two subgroups with different severity according to the presence or absence of MAHA. The detection of complement factor and E-selectin may play a role in differentiating the two subgroups of SLE-TMA. The complement pathway is highly activated in patients with compound complement mutations, resulting in increased complement factors consumption.

Mapping Genomic Regulation of Kidney Diseases and Traits at a Cell Type and Variant Level of Specificity
Christopher Benway, Michelle McNulty, Seong Kyu Han, Dongwon Lee, Matt G. Sampson. Nephritic Syndrome Study Network (NEPTUNE) Consortium, Boston Children’s Hospital, Boston, MA.

Background: Although numerous genetically associated loci for kidney disease and disease have been identified by genome-wide association studies (GWAS), determining the causal genes and functional variants remains a major challenge. Integration of GWAS results with other data types (such as expression quantitative trait loci (eQTLs)) can help identify causal and functional variants in a tissue- or cell-type specific manner. Further, analysis of disease tissue may uncover context-specific associations that may otherwise not be detectable.

Methods: We integrated eQTL data from micro-dissected glomerular (n = 240) and tubulointerstitial (TI) (n = 311) transcripomes from individuals with nephrotic syndrome and summary statistics from two large trans-ethnic GWAS meta-analyses for estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). We used a Bayesian statistical framework for eQTL data integration and mapping (TORUS/DAP). eQTL signals from each renal compartment were integrated with summary statistics to perform a gene-level probabilistic transcriptome-wide association study (PTWAS) and SNP-level co-localization (fastENLOC).

Results: We identified 5,526 glomerular and 9,742 TI eQTLs at >5% FDR level. For eGFR, we identified 971 gene-trait pairs in the glomerulus and 1,816 gene-trait pairs in TI tissue that were significant (FDR < 5%). For UACR, we identified 194 and 340
significant gene–trait pairs in the glomerulus and T1 tissue, respectively. In the SNP-level co-localization analysis, we identified 46 T1 and 3 glomerular co-localization signals (regional co-localization probability [RCP] > 50%) for eGFR, including known associations with UMOD and FGFR5 expression, as well as novel associations to LARP4B and RABG5D which can be attributed to single variants. We identified 7 T1 and 16 glomerular co-localization signals (RCP > 50%) for UACR. In addition to replicating co-localization signals at PRKCI and TGFBI in glomerular tissue, we refined the co-localization signal at PTHFR to a single variant, rs6787229, which also co-localized with expression of MYL3.

Conclusions: Profiling and integrating renal compartment-specific eQTLs with kidney trait GWAS results in a probabilistic framework identified novel gene–trait associations and refined many known associations to a single variant.

Funding: NIDDK Support

PO1367
Factors Contributing to Decisional Conflict in Older Persons Facing Dialysis Decisions

Background: Dialysis and conservative kidney management are the two main treatment options for elderly persons with end-stage kidney disease who are ineligible for kidney transplantation. The high stakes of these decisions often force patients to choose between quality versus quantity of life. Thus, they face tremendous conflict while making dialysis decisions. This decisional conflict can adversely affect their mental health-related quality of life and leads to avoidable delays in decision making. Exploring factors contributing to dialysis decision conflict in older persons with chronic kidney disease is critical.

Methods: Using a qualitative descriptive approach, we purposefully sampled a cohort of 10 patients; 5 with high scores on decisional conflict scale, and 5 with low scores. Patients met with a palliative care physician to discuss dialysis and these visits were audio-recorded. Audio recordings were transcribed verbatim and entered into MAXQDA for data management. Following an iterative process, 2 independent reviewers analyzed the transcripts for common themes contributing to decisional conflict.

Results: The mean age of patients was 83 years. We observed 3 themes in the data of patients with low decisional conflict: (1) clarity in values, (2) good current quality of life, and (3) strong therapeutic alliance with their nephrologist. In the high decisional conflict group, we observed 5 themes: (1) fear of physical pain, complications from dialysis and its time commitment, loneliness, and losing independence, (2) concerns about being a burden to loved ones, (3) uncertainty about prognosis, (4) worries about transportation to and from dialysis, and (5) poor knowledge of treatment options.

Conclusions: Patients with high decisional conflict worried about their future quality of life, sense of burdensomeness, prognostic uncertainty, and issues related to transportation. They wished for detailed knowledge of treatment options. Future dialysis decision-making interventions should be tailored to identify each patient’s unique needs, and incorporate details about treatment options and information about logistics of dialysis. Nephrologists need to discuss the expected quality of life and prognosis. Last, family involvement in these discussions and buy-in for or against dialysis may be helpful in mitigating the patient’s sense of being a burden on their loved ones.

PO1368
Shared Decision-Making Among Older Adults with Advanced CKD
Rebecca Fraizer,1 Sarah Levine,2 Hocine Tighiouart,3 John B. Wong,3 Tamara M. Coch-Weser,1 Elisa J. Gordon,4 Daniel E. Weintraub,4 Keren Ladin,3 1Northwestern University Feinberg School of Medicine, Chicago, IL; 2Tufts Medical Center, Boston, MA; 3Tufts University, Medford, MA.

Background: Older adults with advanced chronic kidney disease (CKD) face difficult, preference-sensitive decisions about dialysis. Although shared decision-making (SDM) can help align treatment with patient preferences and values, the degree to which older CKD patients experience SDM and associated factors remain unknown.

Methods: Using data from the Decision Aid for Renal Therapy Trial, we examined SDM in adults ≥70 years with non-dialysis CKD stage 4–5 from 4 sites in the US using the validated SDMQ9 measure, with scores scaled from 0-100, and higher scores reflecting SDM in adults ≥70 years with advanced CKD and 10 of their clinicians. We also reviewed patients’ electronic health records and abstracted passages containing further information on treatment of their advanced CKD. We used thematic analysis to analyze interview transcripts and note passages and identify emergent themes reflecting their joint decision-making about treatment of their advanced CKD.

Results: Patients (age 73±6 years) were mostly men (60%) and Caucasian (59%). Of the patients (age 52±12 years, 30% male, 70% Caucasian) who participated in interviews, 4 (40%) were non-nephrologists. Four themes emerged from qualitative analysis: 1) Competing priorities: patients and their clinicians tended to differ on when to triage CKD and dialysis planning above other priorities; 2) Focusing on present or future: patients and their clinicians could be misaligned on their outlook on CKD, with patients being more focused on living well now; and clinicians, on preparing for dialysis and future adverse events; 3) Textbook approach to CKD: patients perceived their clinicians as taking a monolithic approach to CKD that was predicated on clinical practice guidelines and medical literature rather than their lived experience with illness, while clinicians were uncertain about how to incorporate patients’ personal values and goals into decision-making; and 4) Power dynamics: while patients described cautiously navigating a power differential between themselves and their clinicians, clinicians seemed less attuned to these power dynamics.

Conclusions: Improving shared decision-making for treatment of advanced CKD will likely require efforts that explicitly reconcile the differences in mindset between patients and their clinicians on decision-making about treatment of advanced CKD and that address the power imbalances in their therapeutic relationship.

Funding: NIDDK Support

PO1370
Effect of Estimated Glomerular Filtration Rate on Survival in Patients 75 Years of Age at Dialysis Initiation
Agnieszka Hamroun,1,2 Linh Bui,3 Sébastien Gomis,1 François Glowacki,1 1Centre Hospitalier Universitaire de Lille, Lille, France; 2Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; 3Paris Saclay University, Paris, France.

Background: Data regarding the prognostic impact of estimated glomerular filtration rate (eGFR) at dialysis start are discordant, and remain very scarce in elderly populations. The aim of this study is to explore whether the effect of eGFR on survival was similar in elderly incident dialysis patients compared with younger ones.

Methods: We included 4690 patients ≥75 years of age and 7045 patients 18-74 years of age starting dialysis between 2004 and 2018 from a French regional registry. Patients were followed until death or the end of 2019. Survival was assessed by Kaplan-Meier curves and the relative risk of death associated with eGFR (MDRD) was assessed by multivariate Cox regression analysis.

Results: The results showed an increasing trend of eGFR at dialysis start, which was also systematically higher in elderly patients (13.2 [10.1; 17.2] vs 11.2 [8.3; 14.9] ml/min/1.73m²; p < 0.001) (Figure). Overall, we found a significant dose-effect relationship between eGFR at dialysis initiation and mortality (HR = 1.33 [1.16; 1.51], 1.47 [1.29; 1.69], and 1.72 [1.49; 1.78] respectively for eGFR [5-10], [10-15], and > 15ml/min/1.73m²; p for trend < 0.001). The same results were found in subgroup analyses according to age category (Figure 2), with a significant interaction in favor of a stronger association in younger patients (p = 0.031).

Conclusions: In incident dialysis patients, our study shows a dose-effect relationship between higher eGFR at dialysis start and mortality, regardless of age category. This association seems to be even stronger in younger patients.
**PO1372**

**Mortality Rates in a Nationally Representative Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis**

Amy S. You,1 Kamyar Kalantar-Zadeh,1 Yoko Narasaki,1 Csaba P. Kovesdy,2 Dana B. Mukamel,1 Susan T. Crowley,1,4 Alejandra Novoa-Vargas,1 Danh V. Nguyen,1 Connie Rhee,1 University of California Irvine, Irvine, CA; 2The University of Tennessee Health Science Center, Memphis, TN; 3Yale University School of Medicine, New Haven, CT; 4Veterans Health Administration, Washington, DC.

**Background:** While dialysis has been the prevailing treatment paradigm in CKD patients progressing to ESRD, this treatment approach may not offer survival benefit nor improved quality of life in certain subgroups (elderly, multi-morbid). Hence, there is growing interest in conservative management (CM) as an alternative treatment strategy in advanced CKD.

**Methods:** We compared mortality rates in advanced CKD patients (eGFRs <25 separated by a90 days) treated with CM vs. dialysis from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-2ys of the index eGFR (1st eGFR <25), with the former group parsed into late vs. early dialysis (eGFRs <15 vs. ≥15 at dialysis transition). Secondary analyses stratified the former group as late, intermediate, vs. early dialysis (eGFRs <5, 5-<10, vs. ≥10 at dialysis transition). Poisson regression was used to compare mortality rates across exposure groups.

**Results:** Among 309,188 advanced CKD patients, 60% vs. 40% of patients were treated with CM vs. dialysis, respectively. Patients who underwent CM vs. late dialysis had similar mortality, whereas those who underwent early dialysis had the highest mortality rates. In secondary analyses comparing CM and late vs. intermediate vs. early dialysis, a similar pattern was observed (140, 126, 141, vs. 158 deaths per 1000 person-yrs, respectively). In age-stratified analyses, compared to CM, all dialysis groups had higher mortality rates irrespective of timing of initiation in those <65 and ≥65 yrs old.

**Conclusions:** In a nationally representative cohort of advanced CKD patients, CM vs. late dialysis demonstrated similar mortality, whereas those who underwent early dialysis had the highest mortality rates.

**Funding:** NIDDK Support

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**PO1371**

**Hospitalization Risk Among Advanced CKD Patients Treated with Conservative Management vs. Dialysis**

Connie Rhee,1 Amy S. You,1 Yoko Narasaki,1 Csaba P. Kovesdy,2 Dana B. Mukamel,1 Susan T. Crowley,1,4 Alejandra Novoa-Vargas,1 Danh V. Nguyen,1 Kamyar Kalantar-Zadeh,1 University of California Irvine, Irvine, CA; 2The University of Tennessee Health Science Center, Memphis, TN; 3Yale University School of Medicine, New Haven, CT; 4Veterans Health Administration, Washington, DC.

**Background:** Regarded as the default treatment option for advanced CKD, dialysis has been associated with frequent hospitalizations, functional decline, and loss of independence, particularly in the elderly and comorbid. While there is rising interest in conservative management (CM) as an alternative treatment option, this strategy remains underutilized. We sought to quantify differences in healthcare utilization in advanced CKD patients transitioning to dialysis vs. CM.

**Methods:** We compared hospitalization risk in 309,188 advanced CKD patients (eGFRs <25 separated by a90 days) treated with dialysis vs. CM from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. We examined hospitalizations within 2yrs of the index eGFR to account for death as competing event for hospitalization.

**Results:** In the overall cohort, 55% and 20% of patients experienced ≥1 hospitalization(s) and death, respectively, within 2yrs of the index eGFR. Patients who transitioned to dialysis were more likely to be hospitalized vs. those treated with CM (77% and 47%), with a larger proportion of hospitalizations occurring pre- vs. post-dialysis transition in the former group (57% vs. 20%). While the proportion of deaths across dialysis vs. CM were similar (18% vs. 20%), the composite endpoint was more frequent in patients treated with dialysis vs. CM (79% and 55%).

**Conclusions:** In a national cohort of advanced CKD patients, while the proportion of death events was similar in those treated with dialysis vs. CM, patients who transitioned to dialysis had higher hospitalization risk. Further studies are needed to compare the components and effectiveness of CM vs. dialysis on CKD outcomes.

**Funding:** NIDDK Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Continued Primary Care Use During the Transition to Kidney Failure (KFRT) Is Associated with Reduced Mortality Among Older Hemodialysis (HD) Patients

Raquel C. Greer, JD; Yoon B. Ahn, Laura Plantinga, John Spertei, Mara McAdams-DeMarco, Kelly H. Beers, Sandeep S. Soman, Michael J. Choi, Bernard G. Jaar.

Background: Primary care providers (PCPs) are responsible for addressing patients’ comprehensive health needs. However, the provision of primary care during the KFRT transition and its contribution to clinical outcomes among in-center HD patients have not been well explored.

Methods: We quantified the associations between PCP use, mortality, and hospitalization among older (age≥67) incident (2008-2014) in-center HD patients using data from the United States Renal Data System. We defined patients’ PCP use 1-year prior and 1-year post-KFRT as “continued” for PCP use pre- and post-KFRT; “initiated” for no PCP use pre-KFRT and PCP use post-KFRT; “discontinued” for PCP use pre-KFRT and no PCP use post-KFRT; or “never used” as no PCP use pre- or post KFRT. We used Cox proportional hazard models and adjusted for confounding by using inverse probability weighting method to estimate hazard ratios (HRs) for all-cause mortality and first all-cause hospitalization up to 2 years post-KFRT.

Results: Among 111,424 patients, 57% had continuity of PCP care, 10% initiated PCP use, 10% discontinued PCP use, and 23% never used PCP care during the KFRT transition. Compared to those who never used primary care during the KFRT transition, those with continued primary care use had a 14% lower risk of mortality. Continued and initiated PCP care post-KFRT transition was associated with a 5-12% higher risk of hospitalization, respectively.

Conclusions: Continued primary care use during the KFRT transition was associated with lower mortality, but a higher risk of hospitalization. Additional studies are needed to determine the aspects of primary care that may be beneficial and which patients are most likely to benefit from continued PCP use.

Funding: Private Foundation Support

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<th>Hazard Ratios for All-Cause Mortality and First Hospitalization by Primary Use during KFRT Transition</th>
<th>Never-used</th>
<th>Discontinued</th>
<th>Initiated</th>
<th>Continued</th>
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<tr>
<td>HR (95% CI)</td>
<td>1.66 (1.56-1.78)</td>
<td>1.05 (1.01-1.08)</td>
<td>0.82 (0.73-0.91)</td>
<td>0.75 (0.70-0.81)</td>
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<td>0.002</td>
<td>0.001</td>
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*Adjusted for age, sex, race/ethnicity, employment, Medicaid, region, neighborhood poverty, neighborhood urban, Kim’s frailty index, Lu’s comorbidity index, pre-KFRT nephrology care

POI375

Predictors of Treatment Discussions in Geriatric Dialysis Patients Who Died

Laura Bywater, Hannah Douglass-Molloy, Matthew A. Roberts, Lawrence Mc Mahon, Kathryn Ducharlet, Eastern Health, Box Hill, VIC, Australia; Monash University Faculty of Medicine Nursing and Health Sciences, Melbourne, VIC, Australia.

Background: Geriatric patients on maintenance dialysis often have a high burden of symptoms and comorbidities with limited prognosis. Therefore, in the setting of declining clinical status, goals of treatment (GOT) discussions are important to inform illness expectations and balance the benefits and burdens of ongoing treatment. This study aimed to identify mortality risk factors that prompt nephrologists to have GOT discussions including dialysis withdrawal.

Methods: A cohort of 95 adult patients ≥65 years, cared for by Eastern Health (Victoria, Australia), who died between 1/1/2016-31/12/2019 was analysed using Fischer’s exact tests to identify psychosocial variables associated with functional decline and mortality.

Results: Mean age was 78 (SD 7.3), with mean dialysis vintage 5 years and average 3.7 admissions in the 12 months preceding death. Mean Charlson Comorbidity index (CCI) was 10 (SD 2.3), with hypertension 78%, T2DM (56%), IHD (56%), cardiac failure (51%), malignancy (34%), peripheral vascular disease (32%) and cognitive impairment (28%) major comorbidities. Almost one third (29%) of patients lived in a nursing facility, 74% used gait aids, and 55% needed assisted transport to dialysis. Median time between GOT discussion and death was 5 months [IQR 1, 11]. Discussions were more likely if patients had high comorbidity (CCI≥5, 57% vs CCI<5, 8%, p<0.05) with no association between GOT discussions and patient age, dialysis vintage, functional status, or specific comorbidities. Advance care plans were completed in 26% and were more likely if a GOT discussion had already transpired (23% vs 4%, p<0.05) or the patient lived in a nursing facility (16 v12%, p<0.05). Deaths occurred in hospital (50%), hospice (19%), or at home (7%). Dialysis was withdrawn median 8 days before death [IQR 6, 11].

Conclusions: Older patients died with significant comorbidities and functional dependency, though only the former prompted GOT discussions. Despite a long-term relationship, nephrologists could improve documentation of future treatment planning with patients to promote patient centered end of life experiences.

POI374

Vascular Access Type and Survival Outcomes in Elderly Hemodialysis Patients

Marisa Roldán, Cátia R. Figueredo, Raquel F. Escoli, Hernâni M. Gonzalves, Centro Hospitalar do Médio Tejo EPE, Unidade de Torres Novas, Torres Novas, Portugal.

Background: The ideal vascular access for elderly hemodialysis (HD) patients remains widely debated. Limited life expectancy and lower arteriovenous access (AVA) maturation rates increase the likelihood of starting HD with a central venous catheter (CVC). The aim of the study was to evaluate the influence of vascular access type in survival outcomes for elderly HD patients.

Methods: Single-center retrospective cohort study of incident HD patients aged > 80 years from January 2010 to May 2021. Patients who recovered renal function or switched to another renal replacement therapy were excluded. Patients were categorized according to their vascular access at the beginning of dialysis: CVC or AVA. Baseline clinical and demographic data were compared among groups. Survival outcomes by the end of follow-up (31st May 2021) were analyzed using Kaplan-Meier survival curves and Cox’s proportional hazards model. Statistical analysis was performed using SPSS (Version 23 for Mac OSX).

Results: The study included 99 patients: 48 (48.5%) were male, 44 (44.4%) diabetic, 60 (60.6%) had ischemic heart disease and 15 (15.2%) peripheral artery disease. Mean Charlson Comorbidity Index was 8.41±1.65 and mean age 85.14±3.98 years. Eleven patients (11.1%) were over 90 years old. Eighty patients (81%) started HD urgently as inpatients. The vascular access at dialysis start was a CVC in 75.8% (n=75) and an AVA in 24.2% (n=24). No statistical differences were found in age, gender, race, comorbidities among groups. During a mean follow-up of 2.3 years, there were 64 deaths, 27 due to infections (12 access-related infections). All-cause mortality (HR [95% CI]: 1.92 [1.05-3.49], p=0.033) and infection-related mortality (HR: 5.87 [3.18-24.94], p<0.017) were significantly higher among patients who initiate HD with a CVC as compared to an AVA.

Conclusions: The ideal vascular access in elderly patients remains controversial. Our results suggest that patients who start HD with a CVC presented higher all-cause and infection-related mortality when compared with patients who start with an AVA. Our study supports the initiative “fistula first” however more studies are needed to confirm the observations.

PO1373

Geriatric Nephrology: New Insights

PO1375

Predictors of Treatment Discussions in Geriatric Dialysis Patients Who Died

Laura Bywater, Hannah Douglass-Molloy, Matthew A. Roberts, Lawrence Mc Mahon, Kathryn Ducharlet, Eastern Health, Box Hill, VIC, Australia; Monash University Faculty of Medicine Nursing and Health Sciences, Melbourne, VIC, Australia.

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Conclusions: Older patients died with significant comorbidities and functional dependency, though only the former prompted GOT discussions. Despite a long-term relationship, nephrologists could improve documentation of future treatment planning with patients to promote patient centered end of life experiences.
POI1376
Nurse-Driven Advance Care Planning in a Hemodialysis Unit in a Veteran Population
Sam Tonthat,1,2 Rebecca Yamark,2 Jocell Fernandez,2 Jennifer Ballard-Hernandez,2 Marysol Cacciata,2 Pankaj Gupta,2 Jolene L. Chen.2,3 University of California Irvine, Orange, CA; Long Beach Veteran Affairs Healthcare System, Long Beach, CA.

Background: Patients with end-stage kidney disease (ESKD) face difficult choices near the end of life. Advance care planning (ACP) allows patients and their providers to plan for treatments that align with patients’ goals. In the US, only 6-35% of all ESKD patients have advance directives (AD). PREPARE is an interactive ACP website that helps patients complete AD and express their wishes regarding medical decisions. The goal of the study was to assess the feasibility and acceptability of using a nurse to facilitate ESKD patients to completing the PREPARE ACP during dialysis.

Methods: Inclusion criteria include patients without a documented AD within the past 3 years. Exclusion criteria are dementia/cognitive impairment, psychosis, deafness, or blindness. Pre and post engagement surveys were completed. Barriers related to navigating the PREPARE website were documented.

Results: Of 55 patients at the dialysis unit, 25 were eligible and 14 were enrolled. All participants are male with mean age of 69. All participants completed their AD within 1 dialysis treatment. In the pre-PREPARE questionnaire, using the Likert scale of 1 to 5 (1 for “not at all” to 5 for “extremely likely”), patients reported a mean score of 4.01 for readiness to talk about end-of-life care to a close family/friend, 4.23 for readiness to talk to a care provider, 4.46 for readiness to express wishes in writing, and 4.61 for readiness to sign official documentation. In the Post-PREPARE questionnaire, on a scale of 1 (very hard) to 10 (extremely easy), patients scored 7.61 for ease, 7.23 for comfortability, and 8.07 for helpfulness. Analysis of PREPARE AD showed that on a scale of 1 (AD goal mainly to extend life) to 5 (to focus on the quality of life), the mean score is 3.06 suggesting that patients value both “extend life” and “maintain quality of life”. Five patients expressed wishes for full care, 6 wanted a trial of resuscitation, and 3 requested DNR. Barriers to using PREPARE included patient difficulty navigating the website without help and using a laptop during dialysis when both hands are not always free.

Conclusions: Our study shows that PREPARE is a feasible method in facilitating ACP during dialysis; however, many patients needed assistance to complete the process. Future studies are needed to apply PREPARE and ACP wishes in the ESKD population.

Funding: Private Foundation Support

POI1377
Dialysis Patients’ Preferences on Resuscitation: A Cross-Sectional Study Design
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Background: End-stage kidney disease is associated with a 10-100-fold increase in cardiovascular mortality compared to age-, sex-, and race-matched population. Cardiopulmonary resuscitation (CPR) in this cohort has poor outcomes and is often followed by increased functional morbidity. Advance care planning (ACP) is an important aspect of patients’ care that is often missed in chronic kidney disease (CKD) and there is growing support for its use. Nephrologists are often involved in end-of-life care decisions as part of the program.

Methods: A 2-center cross-sectional study design. Adults > 18 years undergoing regular dialysis session or clinic visit. Demographic data were collected and baseline for their patients and frequent end-of-life care discussions can provide insight and help in using a laptop during dialysis when both hands are not always free.

Results: Of 55 patients at the dialysis unit, 25 were eligible and 14 were enrolled. All participants are male with mean age of 69. All participants completed their AD within 1 dialysis treatment. In the pre-PREPARE questionnaire, using the Likert scale of 1 to 5 (1 for “not at all” to 5 for “extremely likely”), patients reported a mean score of 4.01 for readiness to talk about end-of-life care to a close family/friend, 4.23 for readiness to talk to a care provider, 4.46 for readiness to express wishes in writing, and 4.61 for readiness to sign official documentation. In the Post-PREPARE questionnaire, on a scale of 1 (very hard) to 10 (extremely easy), patients scored 7.61 for ease, 7.23 for comfortability, and 8.07 for helpfulness. Analysis of PREPARE AD showed that on a scale of 1 (AD goal mainly to extend life) to 5 (to focus on the quality of life), the mean score is 3.06 suggesting that patients value both “extend life” and “maintain quality of life”. Five patients expressed wishes for full care, 6 wanted a trial of resuscitation, and 3 requested DNR. Barriers to using PREPARE included patient difficulty navigating the website without help and using a laptop during dialysis when both hands are not always free.

Conclusions: Our study shows that PREPARE is a feasible method in facilitating ACP during dialysis; however, many patients needed assistance to complete the process. Future studies are needed to apply PREPARE and ACP wishes in the ESKD population.

Funding: Private Foundation Support

POI1378
Evaluation of a Concurrent Hospice-Dialysis Program for Patients with ESRD
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Background: Most dialysis patients are hospitalized in the last month of life, nearly half of whom receive intensive care. Hospice financing poses a major barrier to hospice delivery to dialysis patients, increasing inequities for high-quality end-of-life care. The Concurrent Hospice-Dialysis Program aims to promote timely hospice services for dialysis patients with limited prognosis by offering concurrent hospice and dialysis.

Methods: We conducted a mixed methods study comprised of chart reviews and semi-structured interviews with 10 bereaved caregivers of deceased patients who were enrolled in the Concurrent Hospice-Dialysis Program and 13 clinicians who provided care as part of the program.

Results: Four major themes were identified: 1) Decisional distress regarding stopping dialysis; 2) The option to continue dialysis served as a psychological bridge to hospice; 3) Clear referral process, formal patient education, and care coordination between hospice and dialysis teams facilitated successful implementation; 4) Providing hospice and dialysis promoted goal-consistent care at end-of-life.

Conclusions: Bereaved caregivers and clinicians involved with the Concurrent Hospice-Dialysis Program found the program broadly acceptable and recommended it for patients on dialysis interested in hospice services. They offered suggestions for systematizing and disseminating the program.

Table 1. Key Themes

POI1379
Concurrent Hospice Dialysis: Perspectives on Dissemination
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Background: In the United States, people receiving dialysis have traditionally been unable to enroll in hospice without ceasing dialysis treatments due to policy constraints. Therefore, these patients are often denied the full benefits of quality end-of-life care, either dying in hospitals or spending only a few days on hospice after dialysis is stopped. An alternative model would allow people living with end-stage renal disease (ESRD) to receive hospice services concurrently with dialysis treatments.

Methods: We implemented a concurrent hospice-dialysis program in one health system as a proof of concept. In this project, we sought to build evidence for feasibility and program requirements for extending such programs to other settings across the country. We conducted semi-structured interviews with people living with ESRD, family caregivers, hospice and dialysis clinicians, and health system administrators from the Pittsburgh area and other regions in the U.S. Interviews elicited perceptions of strengths and weaknesses of a scalable concurrent hospice and dialysis program, including barriers and facilitators of implementation across various settings.

Results: We conducted 25 interviews with 2 patients (8%), 3 caregivers (12%), 15 clinicians (60%), and 5 administrators (20%). Preliminary themes include important considerations: 1) Mechanisms and operational definitions for identification of eligible patients; 2) Procedures for decision-making conversations with patients and families; and 3) Protocols for communication between hospice and dialysis teams to coordinate care. Medicare policy and funding restrictions were also frequently discussed as barriers to the program.

Conclusions: Perspectives from patients, caregivers, clinicians and administrators describe critical implementation processes and resources for a successful concurrent hospice and dialysis program. These include the following: clear criteria for patient eligibility, consistent language to use when talking with patients and families, education for both hospice and dialysis teams, and a well-defined plan for care coordination between teams. Future evaluation of such programs may lead to policy change to make concurrent care broadly financially feasible.

Funding: Other NIH Support - Palliative Care Research Cooperative Group (PCRC)
POI380

Dialysis for the Hospice Patient: A Paradoxical Challenge for Palliative Medicine
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Introduction: We present a case of a patient who developed anuric AKI who subsequently needed dialysis while patient and family were also simultaneously interested in hospice. Our case addresses the difficult conversation in prognosticating and hospice eligibility for patients requiring dialysis can be challenging.

Case Description: A 63-year-old woman with hypertension and recently diagnosed metastatic pancreatic adenocarcinoma initially presented for intractable right hip pain and was admitted for emergent palliative radiation. She experienced rapid deterioration including diaphoresis, hypotension and shock and was managed in the ICU until she was later stabilized off pressors and downgraded to the floors. Unfortunately, she had further complications and quickly experienced anuric AKI from ischemic ATN as her serum creatinine rose from 0.8 to 4.9 mg/dL and became significantly volume overloaded with worsening ascites. The decision was to start a trial of dialysis by family, but they also wanted hospice. Questions arose including prognosis and if patient could simultaneously be provided with dialysis during hospice. Given the current model of withdrawing from dialysis for hospice eligibility, the daughters agreed to transition their mother to hospice.

The patient passed prior to leaving the hospital.

Discussion: We present a difficult scenario for the nephrologist as serious illness conversations remain incredibly challenging. We may opt to not take part in these conversations either due to time commitment, not viewing it as a primary responsibility, or not wishing to upset the patient and their families. Also, so much uncertainty in predicting prognosis makes it intimidating. Here, what also needed to be addressed were hospice benefits for the dialysis patient, if any existed. Usually, one is required to withdraw from dialysis to receive hospice care. There have been suggestions in providing a trial or “as needed dialysis” to focus on a patient-centered type of care but unfortunately that could potentially impact quality metrics and Medicare reimbursement for dialysis centers. As such, these ongoing challenges not only require collaboration between Nephrology and Palliative medicine but also changes at the national broader level.

POI381

Kidney Palliative Care in Transplant Recipients with a Failing Allograft
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Background: Kidney transplantation provides longer survival and better quality of life than dialysis for patients with end-stage kidney disease. However, when allografts fail, navigating treatment options can be challenging as patients with allograft failure are older and sicker than when they were transplanted. Kidney palliative care, specialized interprofessional medical care working together with nephrology providers, providing communication, coordination, symptom management, and psychosocial support for seriously ill patients, has not yet been well-studied for those with kidney transplants.

Methods: We conducted a retrospecitive observational study comparing palliative care delivery, patient treatment choices, and clinical outcomes before and after creation of an inpatient kidney palliative care service (KidneyPal) at our institution. We included adult kidney transplant patients with an allograft failure who were ≥18 years of age and died within 2 years after starting KidneyPal. Allograft failure was defined as imminent indication or chronic need for dialysis for more than 3 months.

Results: Fifty-four and fifty-nine patients were included before and after KidneyPal implementation, respectively. For the patients who experienced death with a functioning graft, inpatient palliative consultation frequency was similar before and after the creation of KidneyPal (40% and 33%, respectively). However, for the patients with allograft failure, palliative care consultation increased from 5.9% to 24.1%. Death in the ICU was common (15% vs. 17%), but death in hospice was more frequent (7% vs. 15%) after KidneyPal was created. While palliative care clinicians addressed code status, symptom management, and psychosocial issues throughout the study period, KidneyPal clinicians held more discussions about treatment options for allograft failure (20% vs. 41%).

Conclusions: Our observational study suggests that kidney palliative care may be useful in the context of allograft failure, particularly with regard to ensuring goal-directed shared decision making. Discussing prognosis, goals of care, and care options after allograft failure are palliative skills that may be enhanced by collaboration with a specialty kidney palliative care team.

POI382

Patient Perspectives on Frailty Status Evaluation During Kidney Transplant Assessment
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Background: The concept of frailty garnered attention within nephrology in recent years, given strong associations between frailty status and kidney disease outcomes. There is increased debate on formulating frailty status evaluation during the early stages of assessment for potential kidney transplant recipients. Studies investigating patient perspectives on frailty and frailty status evaluation during transplant assessment are lacking.

Methods: We conducted a qualitative study using cognitive interviews in English for 25 patients aged 65-85 yrs awaiting initial transplant clinic assessment. The interview explored patient understanding of frailty, perspectives on the impact of frailty on transplantation outcomes and whether formalized frailty status evaluation during transplant assessment should be established. An inductive thematic analysis of interviews to identify themes reflecting patients’ awareness, understanding and perspectives of frailty and frailty status evaluation during assessment was performed.

Results: There were 14 Male and 11 Female participants and mean age was 69.6 yrs ± 3.4. Participants were mainly white (n=18) and native English speakers (n=20). 3 prominent themes were identified. 1) Prerequisite awareness of the frailty syndrome and recognition of its strong associations with negative health outcomes. Most participants understood frailty as a composite of declining physical function, reduced ability to perform daily activities and increased comorbidity status. 2) Severe frailty status is associated with older transplant recipients. Many participants felt worse clinical frailty status is correlated with older age, and older transplant recipients generally do not perform as well. 3) Participants expressed the need for clear definitions and limits for frailty, as patients with end-stage kidney disease are likely to progress through several stages of frailty.

Conclusions: Patient education initiatives should continue to expand awareness of frailty and its implications in transplant care. Further work is required to determine an optimal approach to formally evaluate frailty status during transplant assessment.

Funding: Government Support - Non-U.S.

POI383

Differences in Frailty by Sex in Kidney Transplant Candidates
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Background: Frailty prevalence is higher in women, despite the observed protective effect of female sex on mortality in the general population. Understanding whether there are differences in perceived frailty by sex and the differential impact of frailty on outcomes for males versus females is crucial to avoid a sex disparity within the transplant assessment process.

Methods: We analyzed initial frailty assessments for patients enrolled in a multicenter prospective cohort study across 6 kidney transplant referral centers. Frailty was assessed using the Frailty Phenotype (FP, 3 of slowness, weight loss, low activity, exhaustion, muscle weakness), a Frailty Index (FI, including 37 variables across the domains of social function/cognition, function, mobility, and comorbidity), and the Clinical Frailty Scale (CFS, based on clinical judgement). Assessments were performed prior to or shortly after waitlisting. Prevalence of frailty as measured by the FP, FI, and CFS was reported. An unadjusted Cox survival analysis (separately for males and females) was used to assess the effect of frailty on time to death or withdrawal from the waitlist among activated patients.

Results: A total of 767 unique patients had frailty assessments performed between 2016-2021. Patients were predominantly of male sex (64%), white race (82%) and had a mean age of 54±14. The prevalence of frailty for women was not significantly higher by the FP (16% vs 13%, p=0.15) or the FI (48% vs 46%, p=0.38), but was by the CFS (17% vs 12%, p=0.05). Among 325 activated patients, frailty by the CFS was significantly associated with death/withdrawal for men (HR 2.59; 95% CI 1.16-6.79) but not women (HR 1.1; 95% CI 0.48-4.18).

Conclusions: The prevalence of frailty was higher in females when measured by the CFS, but not by a transplant specific FI or the FP. Despite this, frailty was not significantly associated with mortality/withdrawal from the waitlist for female individuals, emphasizing the need to critically evaluate judgement based frailty assessments and their role in the transplant evaluation process.

Funding: Government Support - Non-U.S.

POI384

Changes in Cognition After Kidney Transplantation
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Background: Longitudinal studies examining changes in cognition pre- to post-kidney transplantation (KT) are small, of short duration and do not include comprehensive neuropsychological (NP) testing or comparison with normative data.

Methods: We analyzed pre- to post-KT cognition in 87 ESKD patients listed for KT and compared it to the National Alzheimer’s Coordination Center (NACC) data. We used linear mixed models for longitudinal, repeated NP test measurements, adjusted for for age, practice effect, sex, race, transplant status, and level of education, and assessed cognition pre- to post-KT for the following domains (Logical Memory I, II, and Digit Symbol tests) and secondary (Mini Mental State Exam (MMSE), Digit span, Category Fluency for animals & vegetables, Trail making A & B) outcomes.
Results: Data from 87 ESKD patients (age ≥ 55 years) and 6974 controls (age 64.9 ± 7.9 years) were analyzed. Pre-KT ESKD patients had lower Logit Memory I, II, Digit Symbol, MMSE, Digit Span Backward, and Category Fluency of vegetables test scores (Table 1). There was no difference in scores of Digit Span forward, Category Fluency of animals, and Trail Making A & B between pre-KT ESKD patients and controls. Post-KT, Logit Memory I and II, and Category Fluency animals & vegetables improved, while Digit Symbol, MMSE, and Digit Span backward scores remained lower than controls (Table 1).

Conclusions: Not all cognitive abilities are affected in ESKD. While some test scores improve with KT, others do not. Further studies are needed to understand the mechanisms underlying cognitive impairment in ESKD and to explore interventions to mitigate them.

Funding: Other NIH Support - NIA

Table 1: NP test comparisons in pre- and post-KT recipients and controls

PO1385
Patients Who Are Treated for Secondary Hyperparathyroidism Have a Lower Risk of Incident Dementia
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Background: Almost all patients with end-stage kidney disease (ESKD) have secondary hyperparathyroidism (SHPT). Elevated parathyroid hormone has been reported as a potential risk factor of cognitive impairment. We aimed to study whether the risk of dementia is improved when patients on dialysis receive treatment for SHPT.

Methods: Using data from the United States Renal Data System and Medicare claims, we studied older (aged 66) ESKD patients without known pre-ESKD dementia claims, we studied older (aged 66) ESKD patients without known pre-ESKD dementia and the number of steps/d were -28, (95% CI -61 to 5 min/d), 13, (95% CI 1 to 24 min/d) in the age ≥ 70 group for sedentary and stepping durations ≥ 70 group for sedentary and stepping durations and the number of steps/day (-424, 95% CI -1669 to 820) in the age < 70 group.

Results: Of 189,433 ESRD patients, 65.1% received a treatment for SHPT during ≥ 70 (N =59) versus age < 70 (N=47).

PO1386
Kidney-Metabolic Risk Factors for Cognitive Impairment in Moderate CKD in the BRINK Study: Beyond eGFR and Albuminuria
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Background: Decreased kidney function is a risk factor for cognitive impairment (CI). We sought to identify kidney-metabolic biomarkers beyond eGFR and albuminuria associated with prevalent moderate to severe cognitive impairment (Mod/Sev CI) in a CKD cohort.

Methods: Community-dwelling non-dialysis participants aged ≥ 45 years with CKD (eGFR <60, in mL/min/1.73 m²) were recruited from four health systems. We examined biomarkers including phosphorus, TNFαR1, PTH, calcium, total cholesterol, hemoglobin A1c%, bicarbonate (CO₂), 2,3-DPG, vitamin D, triglycerides, albumin, hsCRP, and measured global and domain-specific cognitive performance. Logistic regression analyses estimated cross-sectional associations between kidney-metabolic measures and global and cognitive-domain-specific Mod/Sev CI at baseline, adjusted for eGFR, urinary albumin-creatinine ratio (UACR, in mg/g), demographics, and comorbid conditions.

Results: Among 436 participants age ≥ 70 years, 16% were Black, mean eGFR was 34 and median UACR. In adjusted models no kidney-metabolic biomarkers were significantly associated with global Mod/Sev CI. However, in cognitive-domain-specific analyses, low bicarbonate (CO₂, <20 mEq/L) was significantly associated with Mod/Sev impairment in memory [OR (95%CI): 3.04 (1.09, 8.47) P=0.03] and with language [3.82 (1.12, 13.0; P=0.03). In addition, lower total cholesterol was associated with impaired executive function [1.12 per -10mg/dL (1.02, 1.23; P=0.02).

Conclusions: Low bicarbonate (acidosis) and lower cholesterol levels in older patients with CKD may be modifiable kidney-metabolic risk factors for Mod/Sev domain-specific CI in CKD. Longitudinal analyses are needed to determine whether low bicarbonate and low cholesterol are associated with cognitive decline.

PO1387
Targeting Sedentary Behavior in Older Adults: Subgroup Analysis of a Randomized Clinical Trial
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Background: Sedentary behavior (spending most of the awake hours in sitting/lying posture) is associated with increased mortality in CKD but few studies have examined the feasibility of interventions targeting sedentary behavior in older adults with CKD.

Methods: The Sit Less, Interact, Move More (SLIMM) Study was a 24-week RCT of an intervention to reduce sedenary duration with stepping duration in participants with CKD. Physical activity was measured using a mid-thigh accelerometer worn for 7 days before baseline and q8 weeks in standard of care (SOC) group (N=54) and baseline and q8 weeks in SLIMM group (N=54). Based on the accelerometer data, SLIMM group was provided instructions on reducing sedenary duration. In this post-hoc analyses, we used mixed model models to compare the effects of the SLIMM intervention in participants age ≥ 70 (N=59) versus age < 70 (N=47).

Results: Age ≥ 70 group compared to age < 70 group had a higher % of Whites and lower % of stage3b-5 CKD (Table 1). While sedentary duration was similar, the older group had lower stepping duration, gait speed and 6-min walk distance (Table 1). In mixed models, there were no significant differences between SLIMM and SOC groups for sedentary (1, 95% CI -0.36 to 0.35), walking (7, 95% CI -0.12 to 0.35), and number of steps/week (-28, 95% CI -61 to 5 min/d), 13, (95% CI 1 to 24 min/d) and 1330, (95% CI 322 to 2338 min/d), respectively.

Conclusions: It is feasible to decrease sedenary behavior In older adults with CKD.

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

Baseline characteristics between age group
PO1388

Association of CKD Stages with Frailty Worsening or Death in Community-Dwelling Older Adults

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Background: Albumin-creatinine-ratio (ACR) and glomerular filtration rate (GFR) have been associated with prevalent and incident frailty. We analyzed the association of the KDIGO CKD stages and frailty status worsening or death in data of the Berlin Initiative Study (BIS).

Methods: Prospective population-based cohort study interviewing participants biannually with a standardized questionnaire. Frailty assessment according to Fried took place at the 3rd and 4th follow-up. Frailty worsening was defined as the transition within a two-year period from robust to prefrail or frail, or from prefrail to frail. Partial proportional odds regression analysis was used to analyze the association between KDIGO CKD stages and the ordinal outcome of no worsening, frailty worsening, or death.

Results: Of 1076 participants with 46% male and mean age 84.3 years, initially 48% were prefrail and 32% frail. After 2.1 (2.0-2.3) years of follow-up 188 (17.5%) had worsened and 111 (10.3%) died. Participants who died were older (88 vs. 83 yrs), were less physically active, had less muscle mass (calve circumference <31: 10% vs. 5%), and were more likely to be cognitively impaired; 92% had a GFR <60 mL/min/1.73m² and 59% had an ACR ≥30 mg/g compared to 72% and 24% in participants who did not worsen, respectively. Baseline characteristics of participants who worsened were similar to participants who did not worsen. In the multivariable model participants in CKD stages G1/2/A2.3 and G3/A1 or higher had about 3-fold higher odds of frailty worsening than in CKD stages G1/2/A1. The odds for death increased remarkably with both higher CKD stage and increasing albuminuria. Wide confidence intervals are likely due to limited sample size/events. Additional adjustment for frailty baseline status did not alter the results.

Conclusions: In older adults, advanced CKD stages but also albuminuria independent of GFR were associated with 2-fold higher odds of frailty worsening independent of death.

PO1389

Role of Klotho in Aging, Relationship with Frailty, Renal Function, and Body Composition

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Background: Reduced expression of the Klotho protein has been associated with premature aging and increased mortality. Our aim is to evaluate the relationships between plasma Klotho levels and frailty, renal function and anthropomorphic parameters.

Methods: We enrolled a cohort of 1250 volunteers aged > 65 years (FRASNET Study) in recreation centers for the elderly, in hospital’s outpatient clinic and in nursing homes. All the volunteers have signed informed consent and subjects with severe cognitive impairment were excluded (MMSE >18). We measured eGFR (CKD-EPI formula) and body composition by impedancemetry. Plasma Klotho was assayed by an ELISA kit on 194 samples. Frailty was classified according to Fried’s criteria.

Results: A positive correlation between plasma Klotho and renal function (eGFR) has been observed (fig. 1). In agreement with what previously observed, in a younger population, we confirmed a reduction of klothemia in the sarcopenic patients (713 vs 791 pg/mL, p<0.0007 in patients with muscle mass <25% centile) and in patients with high visceral fat mass (fig.2). On the other hand, we did not observe different levels of plasma Klotho according to the frailty class or in relation to age.

Conclusions: In our elderly population, the plasma levels of Klotho do not correlate with age. Therefore, our results confirm the relevance of this biomarker in identifying pathological aging, in consideration of its association within the elderly population with CKD, abdominal obesity and sarcopenia (sarcopenic obesity). Klotho expression was demonstrated as an independent predictor of death in a follow up study and was related to many diseases (e.g: cognitive impairment, cardiovascular disease). The relation of plasma klotho levels and renal function is debated, and conflicting results have been published. Our findings evidenced a significative association of plasma Klotho with renal function and body composition.

PO1390

Shrunken Pore Syndrome: Prevalence and Association with Mortality in a Population-Based Cohort of Elderly Women

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Background: Decreased kidney function results in lower clearance and increased plasma concentration of a GFR marker. So far creatinine has been the commonly used GFR marker but cystatin C becomes more common. Shrunken pore syndrome (SPS) is a recently identified kidney syndrome characterized by disturbed filtration of mid-sized molecules (5-30 kDa) compared to smaller ones (<9 kDa) (Fig1). Resulting in increased plasma levels of cystatin C (cysC) compared to creatinine. SPS is associated with increased risk of cardiovascular disease (CVD) and increased mortality risk. So far few data are available about SPS in population-based cohorts.

Methods: 75-yr old women (n=849) from the population-based Osteoporosis Prospective Risk Assessment (OPRA)-x cohort, with follow-up after 5yr and 10yr were studied. eGFR was calculated with the CKD-EPI equation. SPS was defined as eGFRcysC/eGFRratio <0.6 and mortality risk (HR [95% CI]) estimated. Women with sarcopenia or on glucocorticoids were excluded.

Results: Almost 1 in 10 women (9%) had SPS at age 75 but at age 80 the majority of these women had increased their eGFRcysC/eGFRratio >0.6 (range from 0.6-1.0). Women with SPS had higher 10-yr mortality risk compared to those with eGFRcysC/eGFRratio <0.6 (HRadj 1.7 [95% CI 1.1-2.6]). Table 1.

Conclusions: SPS defined as eGFRcysC/eGFRratio <0.6 is common in elderly women and associated with increased mortality. While longitudinal data indicate that the state may be reversible. Our results also confirm other studies and suggest that SPS may be a clinically applicable tool to assess mortality risk in the elderly.

PO1391

Women with SPS had higher 10-yr mortality risk compared with ratios >0.9 (HR
adj 1.7 [95% CI 1.1-2.6]). Table 1.

Conclusions:

1. Women with SPS had higher 10-yr mortality risk compared with ratios >0.9 (HRadj 1.7 [95% CI 1.1-2.6]). Table 1.
2. SPS defined as eGFRcysC/eGFRratio <0.6 is common in elderly women and associated with increased mortality.
3. Longitudinal data indicate that the state may be reversible. Our results also confirm other studies and suggest that SPS may be a clinically applicable tool to assess mortality risk in the elderly.

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

PO1392

SPS (eGFRcysC/eGFRcrea ratio <0.6) is associated with increased 10-yr mortality

Possible pathophysiological mechanisms of SPS (1) reduced pore size and (2) thickening of the glomerular basement membrane

PO1393

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO1391

Molecular Changes Associated with Type IV Collagen Switching in 1-Day-Old Alport Murine Glomeruli

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Background: Alport syndrome (AS) is an inherited disorder caused by pathogenic variants in COL4A3, COL4A4 or COL4A5, which encodes proteins that comprise basement membranes of the ear, eye and kidney glomerulus. Type IV collagen chains assemble as heterotrimers and during glomerular development, α1α2(IV) within the developing glomerular basement membrane (GBM). This “switching” defines the starting point of disease in AS. We aimed to identify the molecular changes at the time of disease initiation in the developing glomeruli of Alport murine kidneys.

Methods: Immunofluorescence (IF) staining was done to identify the GBM distribution of type IV collagen chains in 1 day old COL4A3 knocko (KO) and wildtype (WT) mice. Urine albumin to creatinine ratio (uACR) was also measured. Subsequently, glomeruli from 1 day old (P1) COL4A3 KO and WT mice were isolated by cardiac injection of magnetic dynabeads that embolized to glomerular capillaries enabling their extraction from surrounding tissue. Protein was isolated and subjected to liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis.

Results: IF localized type IV collagen α1 in the GBM, Bowman’s capsule and mesangial matrix in both P1 KO and WT mice. Type IV collagen α5 was present in short segments of some developing GBM in P1 WT but was absent in KO mice indicating switching. uACR was increased in P1 KO (423.61 ± 69.86 mg/mmol) with a p-value of 0.02. LC-MS/MS identified ~400 proteins from glomerular isolates. In males, 2 and 15 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. In females, 543 and 978 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. Pathway analysis revealed alteration in collagen metabolic process, collagen biosynthesis, collagen formation and extracellular matrix organization.

Conclusions: Increased uACR in P1 KO mice showed disease onset at the time of type IV collagen switching. LC-MS/MS analysis revealed dysregulation of matrix turnover pathways in P1 KO mice, identifying potential molecular targets.

Funding: Private Foundation Support

PO1392

PTEN-Induced Kinase 1 Has Association with Renal Aging in the Context of Inflammatory Response

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Background: Among several changes of aging-related human organ system, functional and structural deterioration of kidney is the most dramatic phenomenon, and the role of mitophagy has recently considered important in pro-aging process in CKD patients. PTEN-induced kinase 1 (PINK1), known to be associated with age-related diseases regulates mitochondrial dysfunction. To enhance understanding the function of PINK1 on aging, we compared whole-kidney RNA sequencing between naturally aging mice and PINK1-overexpressing HKC8. We also investigated the function of PINK1 on aging, we used PINK1-deficient mice and PINK1-overexpressing HKC8.

Methods: Kyoto Encyclopedia of Genes and Genomes pathway analysis and gene ontology analysis were performed for gene expression analysis. To investigate the role of PINK1 on aging, we used PINK1-deficient mice and PINK1-overexpressing HKC8.

Results: Compared to naturally aging kidneys, PINK1 knock out aging mice showed prominent expression of the genes related to cytokines, immune system response, and inflammation (Fig 1). We also investigated the function of PINK1 in HKC8 and observed that PINK1 knock out aging mice showed more prominent expression of the genes related to cytokines, immune system response, and inflammation (Fig 2). The quantitative PCR analysis validated the expression of genes associated with aging, fibrosis, and inflammation increased in PINK1(-/-) mice compared to WT mice. Finally, on multivariate Cox-regression analysis, PINK1 expression correlated positively with segmental glomerulosclerosis (p=0.025) and creatinine level at diagnosis (p=0.002), while pSmad3 expression with interstitial inflammation (p=0.024). In glomerulus, concomitant expressions of high Smad7 and medium pSmad3 were observed to be correlated with renal inflammation, such as cellular crescent (p=0.011), intense interstitial inflammation (p=0.029) and lower serum complement 3 (p=0.028) and complement 4 (p=0.029). We also reported a significant association between pSmad3 expression in glomerular endothelial cells of proliferative GN (p=0.045) and in podocytes of non-proliferative GN (p=0.005). Finally, on multivariate Cox-regression analysis, TGF-β1 expression (HR = 6.078; 95% CI 1.168-31.627; p=0.032) was emerged as independent predictor for CKD.

Conclusions: In conclusion, our results suggest that PINK1 deficiency contributes to renal aging process via proinflammatory change in the kidney.

PO1393

TGF-β1/Smad Signaling in Glomerulonephritis and Its Association with Progression to CKD

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Background: Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine, with diverse roles in fibrosis and inflammation, which acts through Smad signaling in renal pathology. We intended to investigate the expression of TGF-β1/Smad signaling in glomerulonephritis (GN) and to assess its role as risk factor for progression to chronic kidney disease (CKD).

Methods: We evaluated the immunohistochemical expression of TGF-β1, phosphorylated Smad3 (pSmad3) and Smad7 semi-quantitatively and quantitatively (computerized image analysis program has also been used) in different compartments of 50 renal biopsies with GN and the results were statistically analyzed with clinicopathological parameters. We also examined the associations among their expressions, the impact of their co-expression, and their role in progression to CKD.

Results: TGF-β1 expression correlated positively with segmental glomerulosclerosis (p=0.025) and creatinine level at diagnosis (p=0.002), while pSmad3 expression with interstitial inflammation (p=0.024). In glomerulus, concomitant expressions of high Smad7 and medium pSmad3 were observed to be correlated with renal inflammation, such as cellular crescent (p=0.011), intense interstitial inflammation (p=0.029) and lower serum complement 3 (p=0.028) and complement 4 (p=0.029). We also reported a significant association between pSmad3 expression in glomerular endothelial cells of proliferative GN (p=0.045) and in podocytes of non-proliferative GN (p=0.005). Finally, on multivariate Cox-regression analysis, TGF-β1 expression (HR = 6.078; 95% CI 1.168-31.627; p=0.032) was emerged as independent predictor for CKD.

Conclusions: TGF-β1/Smad signaling is upregulated with specific characteristics in different forms of GN. TGF-β1 expression is indicated as independent risk factor for progression to CKD, while specific co-expression pattern of pSmad3 and Smad7 in glomerulus is correlated with renal inflammation.

PO1394

ANCA Negative Medullary Angitis

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Introduction: Medullary angitis is a rare cause of renal failure. Most cases of medullary angitis are found to be ANCA positive. We present a rare case of ANCA negative medullary angitis with no identifiable secondary causes.
Steroids. Our patient had an initial improvement in his renal function with subsequent negative medullary angiitis not associated with IgA nephropathy and recent antibiotic use. This is one of the first case reports of ANCA positivity. ANCA negative medullary angiitis has been documented in the literature with recent reports showing IgA nephropathy and recent antibiotics use to be the most common etiologies. Given the rapid progression of the renal dysfunction, we decided to start our patient on high-dose steroids. Our patient had an initial improvement in his renal function with subsequent decline. However, treatment may have afforded time for AVF creation and patient education before the initiation of hemodialysis, which was the main goal of therapy.

PO1395

Calorie Restriction Ameliorates Obesity-Related Glomerulopathy in Adult Zebrafish

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Background: Obesity is a risk factor for chronic kidney disease. The mechanisms by which obesity results in kidney disease are understudied. Zebrafish are an attractive model animal for studying obesity due to their conserved biology and amenability to genetic screening. The effects of obesity on kidney function in zebrafish have not been reported.

Methods: Zebrafish were fed high-calorie and high-fat diets for 8 weeks. Kidneys were evaluated by light and electron microscopy, and the glomerular filtration barrier was assessed by fluorescent dextran permeability. We also tested the ability of calorie restriction to reverse obesity-related defects.

Results: Fish fed a high calorie diet developed glomerulomegaly, foot process effacement, GBM thickening, tubular enlargement (Figure 1) and ectopic lipid deposition after 8 weeks. High calorie feeding resulted in filtration barrier dysfunction. The observed effects resolved after 4 weeks of calorie restriction (Figure 2).

Conclusions: Our study reveals that obese zebrafish recapitulate key aspects of human pathology, and these defects can be reversed with calorie restriction. These findings establish zebrafish as a potential model for the study of obesity-related kidney disease.

Funding: NIDDK Support

PO1397

Automatic Artificial Intelligence-Assisted Glomerulosclerosis Analysis in Mice Models with Glomerulopathy

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Background: Glomerulosclerosis (GS) is a hallmark pathological feature in glomerular diseases. In preclinical research, GS is recapitulated in a number of experimental mouse models with glomerulopathy, and a cross model characterization of GS would add to our understanding of their translatability to human disease. Here, we report GS quantification using an objective and newly developed automated AI assisted image analysis strategy in three mice models with glomerulopathy.

Methods: AI-assisted GS scoring was performed in three mice models with glomerulopathy and to assess drug treatment effects: 1) Diabetic nephropathy in remnAAV-induced hypertensive uninephrectomized db/db mice (DN/HT). Mice received treatment with vehicle, lisinopril, empagliflozin or combination. 2) T.I. injection of nephrotoxic anti-GBM serum (NTS) and 3) Adriamycin (ADR) in healthy mice. Automatic AI-assisted GS scoring was performed as a two-step process on PAS stained image analysis strategy in three mice models with glomerulopathy, and a cross model characterization of GS would add to our understanding of their translatability to human disease. Here, we report GS quantification using an objective and newly developed automated AI assisted image analysis strategy in three mice models with glomerulopathy.

Results: The automated AI-assisted scoring performed with high degree of accuracy and allowed for a large number of glomeruli to be evaluated pr. section (>100). We show that the mice models had very distinct GS profiles. The DN/HT model was most severely affected with highest average GS score (DN/HT: 2.5, NTS: 1.76, ADR: 0.68, control: 0.1) and the largest percentage of severely affect glomeruli, GS+GS4 (DN/HT: 54.1%, NTS: 37.2%, ADR: 16.8%, control: 1.1%). The ADR model was the least affected and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

443
PO1398
Increased Glomerular Parietal Epithelial Cell Expression of Cathepsins C and B in Anti-Thy1.1 Mouse Model of FSGS
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Background: Focal segmental glomerulosclerosis (FSGS) is characterized by replacement of glomerular capillaries by extracellular matrix (ECM). The collapsing FSGS (cFSGS) variant exhibits a poor prognosis and response to therapy. We recently reported that activated PECs migrate into glomerular tufts in human cFSGS and demonstrate increased cathepsins C and B expression. The absence of cathepsins B and C within normal glomerular tufts suggests these proteases may represent novel mediators of PEC-mediated glomerulosclerosis leading to collapse. We addressed the hypothesis that activated PECs expressing cathepsins C and B migrate into glomerular PECs in a mouse model of cFSGS.
Methods: Thy-1.1 transgenic mice were injected with either saline (vehicle control) or 250mg/kg anti-Thy1.1 (19XE5; 1mg/mouse) to induce FSGS. Mice were sacrificed 4, 7, and 21 days after injection. Kidney sections were subjected to immunofluorescence staining for claudin-1, a marker of PECs, and cathepsin C or cathepsin B. Images were acquired by confocal microscopy.
Results: Claudin-1, cathepsin C, and cathepsin B co-localized to glomerular parietal epithelial cells lining Bowman’s capsule in vehicle control mice. On day 4 after anti-Thy-1.1 administration, claudin-1 staining showed migration of PECs into glomerular tufts in more than half of the glomeruli. Both cathepsin B and C staining co-localized to activated PECs within glomeruli. PECs in the Bowman’s capsule with hypertrophied morphology, suggesting activation, demonstrated increased expression of cathepsins C and B. Claudin-1 and cathepsins B and C co-localized within glomeruli on days 7 and 21 after anti-Thy-1.1 administration, however, the number of stained cells per glomerulus and the percent glomeruli with positively stained cells in the glomerular tuft appeared decreased.
Conclusions: Glomerular PECs migrate into glomerular tufts and show increased expression of cathepsins C and B in the anti-thy1.1 model of cFSGS, recapitulating our findings in human cFSGS biopsies. The Thy-1.1 mouse model of cFSGS can be used to define the role of FSGS expression of cathepsins B and C in the pathogenesis of human cFSGS.
Funding: Clinical Revenue Support

PO1399
Effects of Enzymatic Cross-Linking and Increased Stiffness on Glomerular Basement Membrane and Podocyte Function
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Background: The Glomerular basement membrane (GBM) is a critical component of the glomerular filtration barrier. Stiffening of the extracellular matrix is an important regulator of cellular function. How GBM stiffening affects podocyte function is not fully understood. This work aims to investigate the effect of GBM stiffening on molecular permeability and the podocyte function using a biomimetic in vitro model directly derived from kidney glomeruli.
Methods: Decellularized glomeruli isolated from porcine kidneys were pressure crosslinked on a Transwell membrane. GBM stiffness was tuned by crosslinking with transglutaminase (TG). The stiffness of the TG-crosslinked decellularized glomeruli was evaluated using a custom cantilever-based compression system. Podocytes cultured on the TG crosslinked GBM were immunofluorescence stained with YAP, phalloidin and the nuclei counterstained with DAPI. The diffusional molecular permeability was evaluated on native and TG crosslinked GBM with and without podocytes using FITC-Ficoll and AF488-BSA. Effects of GBM stiffening on gene expression of markers of podocyte differentiation (NPEP1, WT1, Synaptopodin) were screened by qPCR.
Results: The stiffness of the decellularized glomeruli showed a dose-dependent increase after incubating with TG for 1 day and 4 days. On stiffer GBM, immunofluorescence imaging showed translocation of YAP to the podocyte nucleus. Passive molecular permeability of GBM was similar for native the TG crosslinked GBM. Podocytes cultured on both native and TG crosslinked GBM forms a stringent barrier to large molecules. qPCR results show an upregulation of differentiation markers as podocytes cultured on native and TG crosslinked GBM.
Conclusions: We developed a biomimetic in vitro model that fabricated directly from kidney tissue. nTG crosslinked glomeruli show a dose-dependent increase of stiffness. TG did not significantly effect the diffusive permeability of the GBM. GBM stiffness affects the YAP localization in the podocytes. The current in vitro model upregulates the gene expression of podocyte markers.
Funding: Other U.S. Government Support

PO1400
Effect of ANG-3070 in the Unilateral Ureteral Obstruction Model of Renal Fibrosis
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Background: Tubulointerstitial inflammation and fibrosis are strong predictors of progression in all kidney diseases regardless of etiology. Receptor tyrosine kinases such as platelet-derived growth factor receptor (PDGFR) and discoidin domain receptors (DDRs), contribute to renal inflammation and fibrosis. ANG-3070 is an inhibitor of multiple tyrosine kinases receptors including PDGFR and DDR. This study evaluated whether ANG-3070 can slow the progression of fibrosis in the unilateral ureteral obstruction (UUO) mouse model of renal fibrosis.
Methods: Male mice were subjected to UUO and randomized to daily oral treatment with vehicle (n=15) or 100 mg/kg of ANG-3070 (n=15) for 10 days after UUO and then sacrificed. Control male animals were age-matched and were not subjected to UUO (n=10). At sacrifice, obstructed and control kidneys were collected and processed for renal damage by hematotxylin-eosin (H&E) staining and scoring (0-8; 0 no damage and 8 damage to >80% of kidney) by blinded observers. Collagen deposition and myofibroblast transformation was determined by quantitative image analysis of picrosiris red (PSR)-stained slides and slides stained for α-smooth muscle cell actin (αSMA), respectively.
Results: Animals treated with ANG-3070 had a statistically significant reduction in histological damage as compared to vehicle (Vehicle, 6.4 vs ANG-3070, 4.3; p-value <0.001) and the histological markers of fibrosis, PSR (% control, vehicle, 1458% vs. ANG-3070, 503%; p-value <0.001), and αSMA (% control, vehicle, 511% vs. ANG-3070, 248%; p-value <0.001) as shown in Figure 1.
Conclusions: Daily oral administration of 100 mg/kg ANG-3070 reduces renal damage and renal fibrosis in a mouse model of renal fibrosis induced by UUO.
Funding: Commercial Support - Angion Biomedica, Inc.

Figure 1
chronicity index was still most powerful risk factor (P<0.05 for all) and they showed similar results to whole CKD stages. There was insufficient evidence to initiate IST according to chronicity index.

**Conclusions:** Among the known prognostic factors of IgAN, pathologic features were relatively abstract compared to other prognostic factors. But the chronicity index, presented as a simple integrated numeric scale, which is independently associated with renal outcome in IgAN, is more easily applicable in estimating renal outcome of IgAN patients.

**PO1402**

Comparison of Glomerular Proteome Profiles of Healthy Human Kidney and Minimal Change Disease Identifies Distinct Targets and Pathways

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**Background:** Minimal change disease (MCD) is a common cause of idiopathic nephrotic syndrome and is characterized by diffuse podocyte foot process effacement. The pathogenesis of MCD remains unclear. We hypothesized that proteomics analysis of glomeruli could identify molecular markers that reflect the pathogenesis of MCD.

**Methods:** We included formalin-fixed paraffin-embedded kidney biopsies from patients with steroid-sensitive MCD (n=9) and normal donor kidneys (n=4). Glomeruli were isolated using laser capture microdissection and HPLC MS/MS was done using Orbitrap eclipse mass spectrometer. After data normalization, groups were clustered using principal component analysis (PCA) and compared by paired t-tests.

**Results:** PCA showed separate clustering of healthy glomeruli and MCD samples (FDR<0.05). Out of the 6729 unique proteins identified in MCD glomeruli, 1088 proteins were significantly differentially expressed compared to controls. Pathway analysis showed upregulation of complement pathway components (C1R, C1S, C1Q&A, C2, C3, C4A, C4B, C5, C7, C8B, C9) and downregulation of carbohydrate and amino acid metabolic pathway enzymes (FBP1, FBP2, ALDOC, ALDOB, AKR1A1, ALDH1A1, ALDH5A1, ACAT1). MCD glomeruli showed a significant reduction in expression of ECM proteins FREM2, FRAS1, CDH12. Surprisingly, the expression of podocyte slit diaphragm-associated proteins (SYNO, NPHS2, CD2AP) was not significantly altered in MCD compared to controls. We did not observe differential expression of MCD associated proteins, KANK, CFL1, CMIP. No peptides from SMDP2L3 or ANGPTL4 were identified in MCD glomeruli.

**Conclusions:** Glomeruli from MCD showed differential proteomic signature compared to healthy human glomeruli. Activation of innate immune pathways including the complement system and loss of extracellular matrix and basement membrane-specific components in glomeruli of MCD are novel observations. The role of these markers in the pathogenesis of MCD needs to be investigated.

**Funding:** Clinical Revenue Support

**PO1403**

Effects of ANG-3070 in a Mouse Model of Alport Syndrome


**Background:** Alport syndrome (AS) is a hereditary kidney disease that presents in childhood and progresses to end stage kidney disease (ESKD) in adolescence. There are no approved therapies. AS is caused by mutations in type IV collagen genes Col4a3, a4 or a5; that result in reduced structural integrity of the glomerular basement membrane, triggering activation of fibrionic cytokines, including platelet derived growth factor (PDGF) and transforming growth factor beta (TGFB1) resulting in profibrotic disease and fibrosis. We hypothesized that an antifibrotic therapy may decrease proteinuria-induced fibrosis, and evaluated ANG-3070, a novel tyrosine kinase inhibitor, in a Col4a3 knockout mouse model of AS.

**Methods:** After confirming the Col4a3 mutation by genotyping, 4-week-old male and female AS mouse were randomized to Vehicle (oral, twice-daily) or ANG-3070 (oral, 25 mg/kg, twice-daily) for 5 weeks (n=12/group). Age-matched, wild-type mice were included (n=9) as a control. Animals were sacrificed after 5 weeks of treatment, after collecting spot urines to measure protein to creatinine ratio (PCR). Renal tissue was analyzed for hydroxyproline (HYP) content, by Western blot for tissue fibrotic markers, and for histopathology using hematoxylin-eosin (H&E) staining for renal damage score and picrosirius red (PSR) staining for fibrosis. All histological analyses were performed blinded by two independent observers using a 0-4 scale (0 being normal, 4 ≥75% injured or stained).

**Results:** ANG-3070 treatment reduced mortality (survivors; Vehicle: 8/12 vs ANG-3070: 12/12). In surviving mice, proteinuria was reduced (mg/ml; Vehicle 6.2 vs ANG-3070 3.1; p<0.05) along with PCR (mg/g; Vehicle 11.1 vs ANG-3070 5.5; p<0.05). There was a reduction in renal damage (Vehicle: 2.6 vs ANG-3070: 1.2; p= 0.002) along with renal fibrosis (Vehicle 2.4 vs ANG-3070 1.2; p<0.001). When kidney lysates were evaluated, HYP content was reduced (mg/kg; Vehicle, 132 vs ANG-3070, 57; p<0.001). ANG-3070 along with fibrosis was related to collagen-I, TGFB1, and p-smooth muscle actin (5SMA) compared to Vehicle-treated Alport mice (p<0.05). Additionally, PDGF expression was reduced (p<0.05).

**Conclusions:** Treatment with a novel tyrosine kinase inhibitor, ANG-3070, was evident in AS mice compared to Vehicle. ANG-3070 may represent a novel therapeutic for AS.

**Funding:** Commercial Support - Angion Biomedica, Inc.

**PO1404**

Mesangial-Cell Activation by Circulating Immune Complexes Consisting of Galactose-Deficient IgA1 and IgG Autoantibodies from Patients with IgA Nephropathy

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**Background:** We and others have shown that immune complexes from the circulation of patients with IgA nephropathy (IgAN) that contain galactose-deficient IgA1 (Gd-IgA1) can induce proliferation of mesangial cells (MC) in culture. Here, we assessed cellular processes and signal transduction in MC after stimulation with CIC.

**Methods:** Quiescent primary MC were stimulated for 15 min at 37°C, with or without inhibitors, with circulating immune complexes (CIC) isolated from sera of 13 patients with IgAN. Cell lysates were analyzed directly, or after immunoprecipitation (IP) with antibodies specific for integrin β1 or PDGFR-β, by SDS-PAGE/immunoblotting for IgA, IgG, phospho-ERK1/2, phospho-PDGFR-β, talin, and Axl.

**Results:** Cell lysates from MC stimulated with CIC and the corresponding IP products of Gd-IgA1 (obtusted) and IgA1 (obtusted) contained IgA and IgG. Amounts of IgA and IgG were significantly reduced by an inhibitor of integrin αβ1 (obtustatin), but not by an inhibitor of integrin c5β1 (RGD), and partially inhibited by a tyrosine-kinase inhibitor (dasatinib). CIC induced phosphorylation of ERK1/2 that was inhibited by obtustatin, RGD, dasatinib, and a Chinese herbal medicine, ShenPeng decoction (SP) that has been used to treat IgAN patients in China. Dasatinib and SP inhibited CIC-induced phosphorylation of PDGF-β and Axl. In IP products of integrin β1 from CIC-activated MC, cytoktoskeleton-associated protein talin, known to activate ERK1/2, was associated with integrin β1. SP blocked binding of talin to integrin β1. In IP products of PDGFR-β, CIC induced association of integrin β1 with PDGFR-β, a process that may subsequently induce activation of MAP kinases. Dasatinib and SP inhibited this association.

**Conclusions:** Integrin αβ1 mediated activation of MC by IgA-IgG CIC; CIC activated multiple protein-tyrosine kinases in MC, leading to MAP kinase activation and cellular proliferation. Some of the inhibitors in this study may provide information about the mechanism of MC activation by the pathogenic CIC and, thus, inform development of future disease-specific therapeutic approaches.

**Funding:** NIDDK Support

**PO1405**

Effect of Mycophenolate and Rapamycin on Pro-Inflammatory and Pro-Fibrotic Mediators in Human Mesangial Cells

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**Background:** A significant proportion of lupus nephritis (LN) patients develop chronic kidney disease. TGF-β1 expression is increased in renal biopsies from LN patients and it plays an important role in kidney fibrosis. We previously reported that mycophenolate and rapamycin inhibited pro-fibrotic processes in resident kidney cells in murine LN. We proceeded to investigate the effect of mycophenolate and rapamycin on inflammatory and fibrotic processes in human mesangial cells.

**Methods:** Growth-factor arrested human mesangial cells (HMC) were incubated with or without exogenous TGF-β1 (10 ng/ml), in the presence or absence of mycophenolic acid (1 µg/ml) or rapamycin (3 ng/ml) for up to 72 h. The effect on inflammatory and fibrotic processes was examined.

**Results:** TGF-β1 increased IL-6 and MCP-1 secretion, and α-smooth muscle actin, collagen and fibronecin expression, in a time-dependent manner, accompanied by increased ERK, mTOR and PI3K phosphorylation (P<0.05, for all). Constitutive IL-6 and MCP-1 secretion was mediated through PI3K phosphorylation, whereas IL-6 and MCP-1 secretion induced by TGF-β1 was mediated through PI3K, mTOR and ERK phosphorylation. Cell activation was mediated through PI3K and mTOR activation, while increased collagen and fibronecin expression was mediated through ERK, PI3K and mTOR. Mycophenolic acid inhibited the secretion of pro-fibrotic and pro-inflammatory cytokines, cell activation, and collagen and fibronecin expression, through suppressing ERK activation. Rapamycin inhibited similar processes through suppression of mTOR and ERK activation. Overall, the inhibitory actions of mycophenolic acid were comparable to that of rapamycin.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.**
Conclusions: Mycophenolate and rapamycin both suppress pro-inflammatory and profibrotic processes in mesangial cells by targeting signaling pathways that overlap partially.

Funding: Government Support - Non-U.S.

POI1406
Collapsing FSGS Is Strongly Associated with Microvascular Injury
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Background: Recent studies have suggested that the collapsing variant of focal segmental glomerulosclerosis (FSGS) might be a common secondary feature in renal disease influenced by microvascular injury. Here, we investigated glomerular and arteriolar microvascular injury in patients with collapsing FSGS, including primary FSGS and HIV-associated FSGS, and compared these lesions to patients with other variants of FSGS.

Methods: Biopsies of patients with FSGS were collected, including primary FSGS in native biopsies or transplant biopsies, as well as HIV-associated FSGS. Cases of FSGS secondary to renal diseases known to be caused by microvascular injury were excluded. We assessed all glomeruli in a biopsy for the presence of lesions associated with FSGS or ischemic injury, assessed microvascular lesions in glomeruli and arterioles, and studied interstitial lesions.

Results: We included 53 cases of FSGS, of which 19 cases with collapsing FSGS, 18 cases with FSGS not otherwise specified (NOS), 11 cases with FSGS tip, 3 cases with perihilar FSGS and 2 cases with cellular FSGS. Compared to other variants of FSGS, glomerular endothelial swelling of the vascular pole was more common in patients with collapsing FSGS (11% vs 0.0%; p<0.05). Associations between thrombotic injury and FSGS variant were not found. Arteriolar abnormalities were seen in 58% of collapsing FSGS and 38% of other variants of FSGS (p=0.17). When evaluating the concomitant occurrence of FSGS lesions and microvascular injury in individual glomeruli, we found that collapsing lesions and FSGS NOS lesions were associated with endothelial swelling in the same glomerulus (OR=22; p<0.001 and OR=3.8; p<0.01, respectively). Endothelial swelling was more common in glomeruli with collapsing lesions than with glomeruli with FSGS NOS (OR=2.7; p<0.044). Collapsing FSGS was also associated with endocapillary hypercellularity (OR=4.3; p<0.001).

Conclusions: Here, we demonstrate that collapsing FSGS lesions are strongly associated with microvascular injury such as endothelial swelling and endocapillary hypercellularity, and often co-exist in the same glomerulus. In addition to collapsing FSGS occurrence, this secondary phenomenon in renal microangiopathies, these results indicate that endothelial injury could also be involved in the pathophysiology of collapsing FSGS due to primary podocyte injury.

POI1407
Danhong Injection (DHI) Inhibits Lipopolysaccharide-Enhanced Cell Proliferation of Rat Renal Mesangial Cells via NF-κB Signaling Pathway
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Background: To explore the mechanisms of DHI in the treatment of Mesangoproliferative glomerulonephritis (MsPGN), we investigated the effects of DHI on LPS-induced NF-κB activation and its downstream inflammatory mediators, such as ICAM-1, TGF-β1, iNOS and FN protein expression in rat MCs.

Methods: The rat MCs treated with different concentrations of DHI (0, 50, 100, 200, 500, 1000, and 2000 μL/L) for 12 h, then incubated with or without 100 ng/mL LPS for another 24 h. Then, cell proliferation was determined by CCK8. The MCs treated with low-dose DHI (250 μL/L), median-dose DHI (500 μL/L) and high-dose DHI (1000 μL/L) for 12 h or PDTC for 30 min before 24 h treatment of LPS. Then the activation of NF-κB was detected by Western blot and immunofluorescence. The protein levels of ICAM-1, TGF-β1, iNOS and FN in rat MCs were detected by Western blot.

Results: DHI significantly suppressed LPS-induced cell proliferation by CCK-8 results (Fig 1). LPS stimulation resulted in a significant increment of p65 contents in nucleus and a decrement of p65 contents in cytoplasm in rat MCs detected by Western blot. PDTC and DHI exerted potent inhibitory effect on increasing expression of p65 in nucleus and decreasing in cytoplasm compared with LPS-treatment group. The inhibitory effect on NF-κB nuclear translocation of DHI was in a dose-dependent manner (Fig 2). The protein level of kβ-β in cytoplasm treated by LPS decreased significantly compared with that in control (Fig 3) and this decrement was significantly reversed by PDTC and DHI. In addition, the protein expression of ICAM-1, TGF-β1, iNOS and FN was also inhibited by PDTC and DHI (Fig 4).

Conclusions: DHI significantly repressed LPS-induced cell proliferation and FN expression in rat MCs through inhibiting the activation of NF-κB signaling pathway also its downstream inflammatory mediators.
Case Description: A 50-year-old woman with a medical history of rheumatoid arthritis, hypertension, and diabetes was treated with a regimen that included hypoglycemic agents and antihypertensives at a treatment center. She was recently diagnosed with hypertension (174/82 mmHg) with elevated serum creatinine (Scr 3.2 mg/dL). She lost follow-up and returned to emergency department 5 months later complaining of worsening edema, fatigue, foamy urine, and joint pain for which she was taking NSAIDs daily. Further workup showed Scr of 8.1 mg/dL (glomerular filtration rate [GFR] 14 mL/min/1.73m²), hyperkalemia (5.5 mmol/L), and hypochloremic metabolic acidosis. A Congo red stain was negative for amyloidosis. She was treated with low dose prednisone (10mg/day) for her RA. Upon follow up it was noted her Scr decreased to 1.4mg/dL but nephrotic range proteinuria persisted.

Discussion: ITG is a rare cause of glomerulopathy. Determining the chronicity and the underlying etiology is essential for the management. This case is associated with RA and presents as a polycystic ITG. The exact treatment for this condition is unknown. Will continue following her closely as historically ITG carries a poor renal prognosis.

POI140
Fibrillary Glomerulonephritis: A Rare Entity, Responsive to Rituximab

Introduction: Fibrillary glomerulonephritis (FGN) is a rare proliferative type of glomerular disease with poor prognosis and limited therapeutic options. Literature review showed very few cases of FGN where Rituximab has been used.

Case Description: A 69-year-old Caucasian woman with a history of DM, HTN presented to the hospital with complaints of dyspepsia and leg swelling. Lab work revealed BUN/Scr of 3433.88 mg/dL (baseline Scr 1.4 mg/dL), proteinuria (7,902 mg/dL). Renal biopsy was performed which showed fibrillary deposits as shown in the picture. Histopathology was consistent with lupus nephritis.

Discussion: The diagnosis of FGN can only be established with kidney biopsy. Most of the patients present with renal insufficiency, nephrotic picture. Mostly idiopathic but can be associated with hepatitis C, dysproteinemia, autoimmune diseases and to lesser extent malignancies. The prognosis is very poor with very limited therapeutic options to date. Immunosuppressive therapy has been used in few cases in literature showing good clinical response. Our patient tolerated and responded very well to Rituximab with significant improvement in kidney function and hence we propose the use of Rituximab in FGN.

POI141
Renal-Limited Lupus Nephritis Misdiagnosed as Advanced CKD: Addressing the Need for Increasing Renal Biopsies in the Community Setting
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Introduction: “Full-house” nephropathy is characteristic of lupus nephritis, but may be seen in patients without other evidence of SLE. Patient was presumed to have acute renal failure and was placed on dialysis for chronic management of ESRD. Despite no extraoral or clinical manifestations of SLE, renal biopsy revealed histopathology consistent with lupus nephritis.

Case Description: A 61-year old African American female presented to an outside hospital with complaints of mild abdominal pain, nausea, emesis, and diarrhea. Family history was positive for autoimmune disorders, including SLE and Sjogren’s Syndrome. Initial lab work revealed creatinine 8.1 mg/dL, eGFR 7 mL/min, BUN 117 mg/dL, proteinuria (7,902 mg/dL). Renal biopsy was performed which showed fibrillary deposits as shown in the picture. Hepatitis panel and work up of malignancy including bone marrow biopsy was negative. She was started on Rituximab 1gm every 14 days for 2 doses. Pt initially required HD but with lisinopril 20mg daily, levetiracetam 500mg twice daily and prednisone 10mg daily. Vital signs were remarkable for uncontrolled blood pressure. Home medications were discontinued unless medically indicated. Hematology was unremarkable. Renal function worsened. Complete blood count was noted to be within normal limits at the age of 24 months. Aging mice also had higher levels of urinary albumin, ACR, and proteinuria. Interestingly, both lysophosphatidic acid (LPA) and phosphatidylserine (PS) abundance were increased in aging glomeruli, suggesting the potential role of LPA signaling in the aging kidney.

Results: These findings suggest that reduced PLPP3 contributes to the accumulation of LPA in glomeruli of aging kidneys. Activation of LPA signaling in glomeruli may play an important role in the pathogenesis of aging-related kidney injury.

Funding: NIDDK Support, Other NIH Support - NIA-San Antonio Nathan Shock Center

POI143
Focal Segmental Glomerulosclerosis: A Rare Cause of Nephrotic Syndrome in Graft vs. Host Disease

Introduction: Nephrotic syndrome (NS) is a very rare complication of allogeneic hematopoietic cell transplantation (HCT) and is usually associated with chronic graft versus host disease (GVHD). In such patients, membranous nephropathy and minimal change disease are the most frequently observed renal pathologies. However, focal segmental glomerulosclerosis (FSGS) is an extremely uncommon etiology in patients with HCT and GVHD. We herein describe a case of a patient with HCT and chronic GVHD who developed NS secondary to FSGS.

Case Description: A 24-year old man with medical history of Sickle Cell Disease status post splenectomy and HCT, epilepsy, arterial hypertension and chronic GVHD with cutaneous and esophageal manifestations who presented to the emergency department with a one month of evolution progressive lower extremity edema and intermittent hematuria. Vital signs were remarkable for uncontrolled blood pressure. Home medications were losinopril 20mg daily, levetiracetam 500mg twice daily and prednisone 10mg daily. Physical examination was remarkable for edema of the lower extremities, ascites, and cachexia. Laboratories revealed: BUN 35 mg/dL, serum creatinine 1.5 mg/dL, total protein 3.00 g/dL, serum albumin 1 g/dL, glucose 110mg/dL, total cholesterol 425 mg/dL, triglycerides 335 mg/dL, VLDL 67 mg/dL and LDL 316 mg/dL. Urine protein/creatinine ratio resulted in 30,000mg/g. Laboratory findings of hypoalbuminemia, hyperlipidemia, and nephrotic range proteinuria were consistent with NS. A renal biopsy was performed and it showed findings consistent with a diagnosis of FSGS, not otherwise specified. Partial remission of NS was achieved at 3 months of treatment with mycophenolate mofetil 500mg twice daily and prednisone 15mg twice daily.

Discussion: GVHD is a significant cause of morbidity and mortality in patients after HCT. Renal involvement can be a serious manifestation and prompt recognition is essential for adequate management and prevention of renal disease. FSGS is an extremely rare complication of HCT and very few cases have been reported in the literature linking FSGS to HCT. Further documentation of this phenomenon is important to further characterize the clinical and pathological features of this complication.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Catastrophic COVID-19-Associated Nephropathy (COVAN) in an Asymptomatic Patient

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Introduction: Glomerular lesions were reported in a minority of patients with COVID-19, with collapsing focal segmental glomerulosclerosis (FSGS) also called COVID-associated nephropathy (COVAN). This typically occurs in the setting of prominent COVID symptoms. We describe a COVAN occurring in an asymptomatic patient.

Case Description: A 48-year-old, African American female patient who had CKD stage 3a secondary to hypertension, with serum creatinine of 1.2 mg/dl and absent proteinuria at baseline, presented to the hospital for evaluation of an asymptomatic elevation of her serum creatinine to 9.9 mg/dl, discovered during a routine evaluation by her PCP. Her urine Protein/ Creatinine was 6.15. Six weeks prior to her presentation, she endorsed 7 days of nausea and intermittent vomiting associated with non-bloody diarrhea without respiratory symptoms. Her GI symptoms has resolved on its own. She had multiple family members, including her husband and daughter, who had tested positive for COVID around the same time. Her nasal PCR for COVID was negative. She had not been vaccinated for SARS COVID. She has no family history of kidney disease; she denied IV drug use and had no risk factors for HIV. She was on Amlodipine for her hypertension. She had 1+ pedal edema with an unremarkable physical exam. A percutaneous kidney biopsy was performed to evaluate the cause of her renal dysfunction. This showed collapsing FSGS. HIV and ANA were negative. There was no evidence of glomerulonephritis. She was on Amlodipine for her hypertension. She had 1+ pedal edema with an unremarkable physical exam. A percutaneous kidney biopsy was performed to evaluate the cause of her renal dysfunction. This showed collapsing FSGS. HIV and ANA were negative. There was no evidence of glomerulonephritis.

Discussion: COVAN is increasing recognized as a serious complication of COVID. However, the typical presentation is in the setting of prominent respiratory involvement. Recognizing the minor fleeting symptoms of COVID preceding a catastrophic kidney disease and testing for it is an important in patients presenting with features of collapsing FSGS.

Siglec-9 Agonism Reduces ANCA-Mediated Neutrophil Responses In Vitro

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Background: Siglec family members, like sialic acid-binding Ig-like lectin 9 (Siglec-9) is constitutively expressed on neutrophils and monocytes. The expression and potential role of siglec-9 in ANCA-associated vasculitis (AAV) is yet to be determined. We aimed to examine the expression of siglec-9 in patients with AAV and explore the impact of siglec-9 agonism on AAV.

Methods: Leukocytes and serum were isolated from peripheral venous blood of AAV patients and siglec-9 expression was measured by flow cytometry and ELISA, respectively. Immunohistochemistry was performed on kidney biopsies of AAV patients with AAGN and stained for siglec-9 and leukocyte markers. Functional studies were done using healthy donor neutrophils in the presence of ANCA and siglec-9 mAb to investigate its role in apoptosis and ROS production.

Results: We found increased serum siglec-9 expression in active AAV compared to remission AAV and a positive correlation with disease activity. Neutrophils and intermediate (CD14+CD16+) monocytes from PR3-ANCA patients displayed higher siglec-9 expression compared to MPO-ANCA patients. Siglec-9 expression in AAGN was restricted to areas of active inflammation. We observed increased siglec-9 shedding in neutrophils following AAGN stimulation. Siglec-9 agonism in these neutrophils was associated with increased apoptosis and reduced ROS production compared to isotype control and unstimulated neutrophils.

Conclusions: Our study suggests that siglec-9 expression correlates with disease activity in AAV. Our functional studies support a potential role for siglec-9 in modulating AAV

Proteinase 3-Alpha1-Antitrypsin Connection in PR3-ANCA Vasculitis

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Introduction: The Proteinase 3-Alpha1-Antitrypsin Connection in PR3-ANCA Vasculitis

Methods: We assessed PR3 and AAT in 100 AAV patients and 50 healthy controls (HC) and produced recombinant wt- and mut-AAT to study the effect on proteolytic PR3 activity, membrane PR3 (mPR3) by flow cytometry and surface plasmon resonance (SPR), and neutrophil activation.

Results: In active PR3- and MPO-AAV, plasma PR3 concentration increased approximately 5-fold and plasma AAT 1.8-fold shifting the PR3:AAT ratio significantly towards PR3. Both parameters normalized with remission. Notably, only one PR3-AAV remission patient showed strongly decreased plasma AAT. The PR3 neutrophil content was approximately 50% higher in active PR3- and MPO-AAV accompanied by increased PR3 translocation. The resulting total PR3 pool (plasma PR3 concentration + PR3 inside neutrophils) was increased by 2.5-fold in active PR3- and MPO-AAV.

Conclusions: We found a strongly increased PR3 pool in active PR3-AAV and decreased plasma AAT as the general underlying disease mechanism, as previously proposed. However, AAT controls mPR3 expression and subsequently PR3-ANCA induced neutrophil activation, suggesting adjunctive AAT administration may have beneficial effects in acute PR3-AAV.

Funding: Government Support - Non-U.S.

Serum Soluble CD206 Complements Urinary Soluble CD163 in Detecting Active ANCA-Associated Glomerulonephritis

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Background: Early detection of active glomerulonephritis (GN) in anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) is crucial to minimize renal damage, but accurate biomarkers are currently lacking. Urinary soluble CD163 (usCD163) has been shown as a potent biomarker for active ANCA GN. However, false negative rates can be as high as 29%. Here, we investigated whether serum soluble CD206 (ssCD206; macrophage mannose receptor), complements usCD163 in the detection of active AAV.

Methods: Three independent cohorts (C1-Maastricht University Medical Center, C2-University Medical Center Groningen & C3-Trinity College Dublin) with available serum, urine, and renal biopsy samples (C1 only) were included. usCD163/creatinine (ng/ml/mg) and ssCD206/creatinine (ng/ml/mg) were assessed by ELISA in urine and serum, respectively. The performance of usCD163 and ssCD206 to detect ANCA GN was assessed using receiver operating characteristics (ROC) curves. Biopsies from ANCA GN patients were immunohistochemically (IHC) stained for CD163 and CD206. Colocalization of CD163 and CD206 was assessed by immunofluorescence (IF).

Results: Patients C1/C2/C3 had active ANCA GN (n=42/17/47), active non-renal AAV (n=3/3/12) or were in remission (n=4/8/38). Healthy controls (HC; n=63/40) were included. usCD163 was significantly higher in active ANCA GN compared to active

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Underline represents presenting author.
non-renal AAV and remission in all cohorts, and healthy control urine in C1 (Kruskal-Wallis, P=0.001). ssCD206 was significantly higher in active ANCA GN compared to HCs in cohorts C1 & C2 (Kruskal-Wallis, P=0.01). ssCD163 had a specificity of 100% in all cohorts, whereas sensitivity was 71 (C1), 88% (C2) and 64% (C3). The addition of ssCD206 increased the sensitivity to detect active ANCA GN in all cohorts to 83% (C1), 100% (C2) and 81% (C3). IHC revealed CD163+ and CD206+ cells in the kidneys of active ANCA GN patients (n=8). IF showed glomerular presence of CD163+CD206- cells, whereas CD163+/CD206+ and CD163+/CD206+ cells were mainly found in the tubulointerstitium.

Conclusions: ssCD206 complements ssCD163 and reduces false negative rates in the detection of active ANCA GN. Histological assessment revealed distinct glomerular and tubulointerstitial populations of CD163+ and CD206+ cells.

POI1419
Alterations in Amino Acid and Lipid Metabolism in ANCA-Stimulated Monocytes
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Background: Multiple metabolic pathways and intermediates are involved in inflammation. Altered immune cell metabolism is involved in the pathogenesis of autoimmune diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). In particular, monocytes stimulated with ANCA show increased oxidative phosphorylation and glycolysis, with a more profound response to myeloperoxidase (MPO) ANCA than proteinase-3 (PR3). The aim of this work was to profile the metabolome of ANCA-stimulated primary monocytes.

Methods: Monocytes from healthy donors (n=24) were isolated and stimulated with mononclonal anti-MPO, anti-PR3 for 4 hours. Metabolites were extracted using an optimised extraction protocol and analysed by liquid chromatography–mass spectrometry (LC–MS). Targeted and untargeted analyses were carried out using Agilent MassHunter Profinder and Mass Profile Reporter. Cytokine production was measured by ELISA and flow cytometry was used to assess surface expression of MPO and PR3.

Results: Targeted metabolomic analysis showed increases in several amino acid and TCA cycle metabolites relative to unstimulated cells, notably phenylalanine, isomers leucine & isoleucine, and fumarate. Untargeted analysis confirmed alterations in amino acid and lipid metabolism in ANCA-stimulated monocytes (Figure 1). These metabolic differences did not correlate with the increased cytokine expression observed in anti-MPO-treated monocytes. Anti-PR3 stimulation did not induce major changes in metabolism or cytokine production. Monocytes expressed high levels of surface MPO and PR3, with MPO expression showing a significant inverse correlation with age.

Conclusions: Inflammatory and metabolic activation of primary human monocytes is greater with anti-MPO, but not anti-PR3 stimulation. Early increases in amino acid and lipid metabolism are evident in anti-MPO treated cells. Further work is needed to validate these findings and determine their physiological relevance in AAV.

Funding: Commercial Support - Agilent Technologies Ireland Limited

POI1420
LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) Are Important for Mediating Myeloperoxidase-ANCA Glomerulonephritis in a Preclinical Mouse Model
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Background: Neutrophils play a critical role in the pathogenesis of necrotizing crescentic glomerulonephritis (NCGN) caused by anti-neutrophil cytoplasmic autoantibodies (ANCA). LFA-1 and Mac-1 are β2-integrins that have critical synergistic roles in neutrophil-mediated inflammation. In this study, we investigated the role of LFA-1 and Mac-1 in murine NCGN induced by mouse anti-mouse MPO, which is histopathologically indistinguishable from human ANCA NCGN.

Methods: Anti-MPO IgG was purified from sera of MPO knock out (KO) mice immunized with murine MPO. Mice with KO of LFA-1 or Mac-1, and normal wild-type C57BL/6j mice (WT B6) were injected i.v. with 50µg/g body weight anti-MPO IgG. Circulating anti-MPO IgG (MPO-ANCA) was monitored by ELISA. Proteinuria, hematuria, and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for pathologic examination. MPO-ANCA-induced neutrophil activation was assayed in vitro.

Results: At day 6, WT B6 (n=9), LFA-1 KO (n=8) and Mac-1 KO (n=9) mice that received anti-MPO IgG had similar levels of circulating MPO-ANCA. All WT B6 mice developed hematuria and NCGN with mean 13.9% glomeruli with crescents and 5.3% with necrosis. In contrast, LFA-1 KO mice and Mac-1 KO mice had normal urine and substantially reduced NCGN (Table). In vitro assays showed that anti-MPO IgG caused similar activation of neutrophils from LFA-1 KO, Mac-1 KO and WT mice.
Conclusions: Depletion of LFA-1 or Mac-1 blocks MPO-ANCA induced NCGN in mice, thus both of these β2-integrins are required for ANCA disease induction. Depletion of LFA-1 or Mac-1 does not block MPO-ANCA induced neutrophil activation. These observations indicate that blockade of either of these β2-integrins abrogates MPO-ANCA NGCN by inhibiting the recruitment of neutrophils that is required to induce inflammatory vascular injury in ANCA disease. These data suggest that pharmacologic blockade of β2-integrins may have a therapeutic role in ANCA disease.

Funding: NIDDK Support

Anti-MPO IgG1-Induced Glomerular Lesions in Different Strains of Mice

POI421

Drilling into a Potential Correlation Between ANCA-Associated Vasculitis and Natural Gas Wells

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Background: ANCA-associated vasculitis (AAV), a systemic necrotizing disease affecting small and medium blood vessels, is caused by antineutrophil cytoplasmic autoantibodies which include anti-proteinase 3 (PR3) or myeloperoxidase (MPO). The incidences of PR3-AAV and MPO-AAV vary geographically with PR3-AAV most commonly reported in the United Kingdom and MPO-AAV the predominant type seen in Japan. Environmental exposure has been implicated in the pathophysiology of MPO-AAV. The aim of this study is to evaluate a potential relationship between AAV and environmental factors in north central West Virginia.

Methods: This is a retrospective cohort study of 212 patients diagnosed with AAV at West Virginia University and its affiliated hospitals from January 1, 1990 to December 31, 2019. Patients were mapped by zip code and prevalence of AAV assessed over time.

Results: The proportion of MPO-ANCA cases increased (37.5% before 2010 vs 71.7% after 2016 (p=0.008)) with a resultant increase in the prevalence of AAV overall after 2010 (Table). During this time, the production of natural gas through fracking increased with barreled production rising more than 5-fold after 2010. Regional heat mapping reveals that the increase in cases of AAV occurred in areas of increased fracking activity (Figure)

Conclusions: The increase in prevalence of MPO-ANCA AAV correlates temporally and geographically with escalations in fracking activity. These findings suggest that exposure to toxins from fracking could be operative in the pathophysiology of AAV and the increase in case numbers seen in north central West Virginia.
Immune Checkpoint Molecule BTLA Attenuates Inflammation and Glomerular Damage in Experimental Glomerulonephritis

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Background: An imbalance of pro- and anti-inflammatory signals in the kidney can result in irreversible damage and destruction of glomeruli leading to end stage kidney disease. Current treatment of the glomerulonephritis (GN) consists of unspecific, highly toxic immunosuppressive therapies with detrimental adverse effects. More specific therapies are therefore warranted. T Lymphocytes are not only key players in the nephrotic nephritis (NTN) model in rodents but also during GN in humans, representing potential targets for tailored therapies. As an immune checkpoint molecule, B and T lymphocyte attenuator (BTLA) is crucial in the regulation of T Lymphocyte activation and has been shown to mediate anti-inflammatory effects in other T cell-mediated disease models.

Methods: NTN was induced in BTLA knock out mice (BTLA-KO) and littermate controls. Regular urine analysis (ACR) was performed throughout the course of the disease. 14 days after NTN induction, blood, kidneys and spleens were harvested for further analysis. Histological assessment of the kidneys was used to evaluate the severity of NTN. Local immune response in the kidney and systemic immunity was analyzed via flow cytometry and qPCR.

Results: Wild type mice (WT) showed an increased BTLA expression on renal T cells and dendritic cells throughout the course of NTN. No immune-phenotype was observed in unstimulated BTLA-KO and WT mice. However, BTLA-KO resulted in aggravation of NTN compared to WT. Quantification and characterization of renal immune cells revealed an increase in proinflammatory cells. Interestingly, especially T Lymphocytes were significantly expanded in BTLA-KO mice.

Conclusions: BTLA attenuates inflammation in experimental GN through suppression of proinflammatory T Lymphocytes. These results build the foundation of a checkpoint inhibitor based therapy of inflammatory glomerular disease.

Collapsing FSGS or Crescentic GN or Both: A Diagnostic Challenge

Mahfuz Irshadjahan

Introduction: The finding of an ANCA associated necrotizing & crescentic GN with collapsing FSGS is a rarity with only few reported cases in literature.1,2

Case Description: A 53-yr-old AA female was admitted to hospital with difficulty in swallowing, poor oral intake, hemoptysis & AKI superimposed on CKD-III with hx of HTN & use of NSAIDs. Urine analysis showed hematuria, proteinuria & UPC ratio of 4.15. Blood analysis showed Hct 8.7mg/dl, BUN 60mg/dl, Albumin 2.4mg/dl, positive MPO ANCA & ANA titers. By light microscopy 36 glomeruli were present, 20% showed arterionephrosclerosis (ischemia) are the most likely etiologies for the collapsing FSGS.

POI426

CD11b Activation Suppresses Pro-Inflammatory IL-1β in Myeloid Cells and Protects Against Lupus Nephritis

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Background: Lupus nephritis (LN) is a debilitating glomerular disease and a comorbidity of systemic lupus erythematosus (SLE). CD11b, the alpha-chain of integrin CD11b/CD18, plays a critical role in cell signaling. Mutations in the ITGAM gene, encoding CD11b, are associated with LN and reduce integrin function. Interleukin-1β (IL-1β) is produced by myeloid cells as a propoerin and cleaved by caspase-1 where it mediates the inflammatory response. IL-1β is downstream of toll-like receptor and IL-1β receptor signaling. We previously showed that activation of CD11b suppresses TLR-dependent pro-inflammatory signaling. Here, we investigate if this mechanism includes control of IL-1β and/or if CD11b influences IL-1β by another mechanism, which may provide novel therapeutic options for proinflammatory diseases.

Methods: To investigate TLR-dependent signaling affected by CD11b activation, we utilized in vitro assays using primary macrophages. Cells were treated with TLR agonists, IL-1β protein, or IL-1β antibody and changes in protein expression was assessed by western blot and proinflammatory cytokine levels were assessed by ELISA.

For complementary in vivo studies, we utilized our newly generated mouse model, where we incorporated a constitutively active CD11b point mutation (I32G) globally in mice to generate a model for CD11b activation – CD11b knock-in model. CD3βL-β wild type mice, CD11b knock-out, and CD11b knock-in mice were used to determine the effect of CD11b activation on circulating IL-1β levels.

Results: TLR-stimulation increased IL-1β levels in vitro and in vivo. Importantly, CD11b activation resulted in significantly reduced IL-1β levels in both systems, suggesting a novel mechanism for controlling inflammation in glomerular diseases. Additional mechanistic studies are on-going to define the exact molecular mechanism of action. Murine models of SLE and LN display significant decreases in IL-1β when CD11b is activated, both genetically or pharmacologically, showing potential protection against LN.

Conclusions: Using these models, we have identified a possible link between CD11b activation and IL-1β secretion in myeloid cells. These studies will provide understanding of the influence CD11b has on signaling pathways and inflammation associated with inflammatory diseases such as LN.

Funding: NIDDK Support

Deletion of Smad3 Worsens Lupus Nephritis by Promoting B Cell Activation

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Background: TGF-β signaling has been shown to play a critical role in many autoimmune diseases. However, its regulatory role in lupus nephritis remains unknown, which was investigated in the present study in a mouse model of lupus nephritis (LN) in which Smad3 gene was deficient.
**Methods:** To investigate the role of Smad3 in LN, we generated Smad3 knockout (KO) lupus mice by cross-breeding Smad3KO mice with B6.NZMSle1-3 lupus mice (C57BL/6J background) mouse. We then determined the regulatory role of Smad3 in the pathogenesis of LN and investigated the regulatory mechanisms of Smad3 in T cell and B cell activation and autoantibody production in Smad3 KO LN and Smad3 WT LN mice and B cells in vivo and in vitro.

**Results:** We successfully deleted the Smad3 gene from B6. NZMSle1-3 mice with unexpected findings that Smad3KO-LN mice developed much more severe LN with higher mortality rate (50%), higher circulating anti-dsDNA (60%), higher levels of serum creatinine (Cr), lower creatinine clearance rate (Ccr, 20%), more severe glomerular necrosis (50%), massive renal immune complex deposition and complement activation, and progressive renal inflammation and functional injury. Mechanistically, we observed that lupus mice lacking Smad3 largely promoted Th1, Th2 and Th17 populations which were directly associated with immune responses in the kidney. Unexpectedly, deletion of Smad3 largely increased macrophage inducible lectin-receptor (Mlec) expression by B220+ B cells (80%). Further studies showed that B cells lacking Smad3 were largely promoted Cytosine-phosphorothioate-guanine oligodeoxynucleotides (CpG ODN)-induced but failed to respond to the inhibitory effect of TGF-β1. Smad3KO-LN mice developed much more severe LN with higher mortality rate (50%), higher circulating anti-dsDNA (60%), higher levels of serum creatinine (Cr), lower creatinine clearance rate (Ccr, 20%) and more severe glomerular necrosis (50%) compared to WT LN mice.

In Conclusion: TGF-β1/Smad3 signaling plays a protective role in LN by maintaining the balance of T cell immunity and B cell function. Loss of Smad3 worsens LN by shifting Treg to Th1, Th2 and Th17 and promoting B cell activation and autoantibody production via the Mlec-Syk-NFκB-dependent mechanism. Thus, outcomes from this study will be of great significance both scientifically and clinically.

**Funding:** Government Support - Non-U.S.

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**POI1428**

**Intrarenal B Cells in Systemic Lupus Erythematosus Upregulate Na+K+-ATPase to Facilitate Survival in a High-Sodium Environment**

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**Background:** The kidney is a unique microenvironment characterized by high sodium concentrations, yet susceptible to infiltration by lymphocytes in autoimmune diseases, such as systemic lupus erythematosus. The effects of sodium-immune cell interactions on tissue injury in autoimmune disease and the mechanisms used by infiltrating lymphocytes to survive the high sodium environment of the kidney are not known.

**Methods:** We investigated the mechanisms utilized by B cells from lupus-prone mice to survive in a high Na+ environment in vitro and in vivo. We also utilized biopsies from lupus nephritis patients to confirm our key findings.

**Results:** Here we show that numbers of kidney infiltrating B cells in murine lupus are significantly decreased when exposed to elevated sodium concentrations [Na+] in vitro and that the expression of sodium potassium ATPase (Na+-K+-ATPase) correlates with the ability of infiltrating B cells to handle sodium stress. Pharmacological inhibition of Na+-K+-ATPase and a genetic knockout of the Na+-K+-ATPase gamma subunit, newly shown by us to be expressed in B cells, resulted in decreased kidney B cell infiltration and amelioration of proteinuria. Na+-K+-ATPase gamma subunit expression was also observed in renal B cells in human lupus nephritis.

**Conclusions:** These studies reveal that kidney-infiltrating B cells in lupus adapt to environmentally regulated sodium stress and identify Na+-K+-ATPase as a novel organ-specific therapeutic target in lupus nephritis.

**Funding:** Other NIH Support - NIH grants R37 AR40072 and R01 AI152443, Private Foundation Support

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**POI1429**

**Environmental Factors Influence Site and Magnitude of Myeloperoxidase-dNA Autoimmunity in BXSB Murine Lupus**

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**Background:** SLE is a systemic autoimmune disease with devastating clinical manifestations and complex origins linked to gene-environment interactions. To better understand the role of environmental factors, we exposed lupus-prone female mice to crystalline silica (Si) or vehicle (V) by oropharyngeal aspiration (OPA), mimicking an inhalational exposure compellingly linked to human autoimmunity. Si but not V exposure compelled an autoimmune glomerulonephritis, uniquely demonstrated elevated anti-myeloperoxidase (anti-MPO) and anti-DNA Ig, are recruited to the lungs, where they can be activated by co-exposure to exogenous or endogenous TLR-L.

**Funding:** Other NIH Support - NEIHS, Veterans Affairs Support

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**POI1430**

**Anti-SOD2 Antibodies in Lupus Nephritis as Second Wave Antibodies**

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**Background:** Superoxide dismutase-2 (SOD2) is an enzyme with antioxidant action. Anti-SOD2 antibodies (anti-SOD2 IgG2) were recently described in the serum of subjects with Membranous Nephropathy, as antigens of a possible second wave injury. The presence of anti-SOD2 IgG2 correlated with worse outcomes in terms of response to treatment [1]. The presence and role of anti-SOD2 IgG2 in Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN), a secondary autoimmune glomerulonephritis, are to be clarified.

**Methods:** We measured serum levels of anti-SOD2 IgG2 (Homemade designed ELISA), every six months, in 1,052 patients (459 LN and 573 SLE) enrolled at different times from the diagnosis (i.e., 0-1 month, 2-12 m, 13-24 m, 25-48 m, 49-96 m, and >96 m).

We also evaluated the main markers of the SLE activity, such as serum complement C3 and C4, ANA, ENA, anti-dsDNA and proteinuria. Of note, 91 LN and 130 SLE had a relevant follow-up of 36 months.

**Results:** As main characteristics, we report median age of 40 (IQR 28-54) years, the predominance of females (88%), disease activity (SLEDAI) of 4 (IQR 2-8). At the cross-sectional analysis, serum levels of anti-SOD2 IgG2 at T0 are significantly higher in LN than in SLE (Fig 1a). Considering LN, the serum levels of anti-SOD2 IgG2 at T0 were significantly higher than the other time points (Fig 1a).

**Conclusions:** Circulating anti-SOD2 IgG2 are elevated in active LN. Serum levels of Anti-SOD2 IgG2, also considering the concomitant negative serum levels of anti-dsDNAs in all phases of LN, support the hypothesis of direct involvement of anti-SOD2 antibodies in LN as second wave antibodies that actively contribute to the manifestations of autoimmune glomerulonephritides.

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**Results:** Si but not V exposed BXSB mice developed chronic lung injury (scores 5.0±4.1 vs. 0.1±0.4) and lung TLS (counts 36±19 vs 6±10), n=13/group, p<0.0001. Levels of anti-DNA and anti-MPO IgM and IgG in BALF and anti-DNA IgG in serum were elevated in Si vs V exposed mice (p<0.05, for each). Spleenocytes produced little anti-MPO or anti-DNA Ig when cultured with medium and abundant anti-MPO IgM and anti-DNA IgG when cultured with TLR-L stimulation, regardless of Si vs V exposure (p=N.S; n=13/group).

Anti-DNA IgG levels were higher from stimulated splenocytes of Si-exposed mice (OD 0.08±0.05 Si vs 0.03±0.01 V, TLR4-L, p<0.0009). Lung cells from Si but not V exposed mice produced abundant autoAb after TLR-L stimulation (OD 1.23±1.100 Si vs 0.025±0.043 V, anti-MPO IgM; OD 0.012±0.010 Si vs 0.001±0.001 V, anti-DNA IgG, TLR7/9-L, p<0.05).

**Conclusions:** Inhaling Si exposure enhances local and systemic autoimmunity in lupus-prone BXSB mice. Autoreactive B cells with diverse disease-relevant specificities, including anti-MPO and anti-DNA Ig, are recruited to the lungs, where they can be activated by co-exposure to exogenous or endogenous TLR-L.

**Funding:** Other NIH Support - NEIHS, Veterans Affairs Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

*Underline represents presenting author.*

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452
PO1431

Altered Proaponeurotic Metabolism and gut Lachnospiraceae Composition in Lupus Nephritis Patients

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Background: There are growing evidence for the role of gut microbiota in the pathogenesis systemic lupus erythematosus (SLE), especially lupus nephritis (LN). Recently, high abundance of Ruminococcus gravisus belonging to the family Lachnospiraceae has been noticed in fecal sample of LN patients. However, the functional role of gut microbiota and its metabolic pathway which affect host metabolism in LN are less understood.

Methods: Shotgun sequencing of fecal samples from biopsy-proven LN patients and matched controls was performed. We used Kraken2 for taxonomic analysis and humann2 with customized KEGG database for gene family analysis. Comparison of taxonomic abundance and gene families were assessed by Maaslin2.

Results: Control and LN group were included 24 and 20 patients, respectively. Both groups had similar age, sex, and eGFR. In the comparison of relative abundance of major species, Roseburia intestinalis, Butyrivibrio fagi, and Eubacterium eligs were significantly decreased while Ruminococcus gravisus was significantly elevated in LN group, respectively. Interestingly, 3 of these 4 species were included in the same Lachnospiraceae family showing a significantly different composition between the two groups (PERMANOVA p=0.042). Furthermore, we found 161 differentially expressed gene families including 65 metabolism-associated and 29 carbohydrate metabolism-associated genes. Considering Lachnospiraceae is known to play a role in proaponeurotic (esters of propionate) formation, we further assessed the proaponeurotic pathway (ko00064).

As a result, LN patients revealed more prone to proaponeurotic pathway rather than in succinate pathway in the proaponeurotic pathway. This tendency was more pronounce in the contribution to the p-value: gene by R. gravisus having well-known pathogenetic linkage with SLE.

Conclusions: LN patients showed altered proaponeurotic metabolism associated with the differential species composition of Lachnospiraceae including R. gravisus. Functional role of this alteration on the pathogenesis of LN should be clarified by further investigations.

PO1432

Gut Microbiome Changes in NZBWFI/J Murine Lupus Nephritis

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Background: Lupus nephritis is an important cause of acute kidney injury and chronic kidney disease. There is preliminary data that gut dysbiosis may be involved in the pathogenesis of lupus nephritis. We investigated gut microbiota burden in murine lupus nephritis.

Methods: Eight-week old NZBWFI/J mice were randomized to receive drinking water alone or containing ampicillin (1.0 mg/ml) and neomycin (0.5 mg/ml) for 18 weeks. Mice with active nephritis showed increased gut permeability to LPS-FITC given orally, and decreased ZO-1 expression in the colonic epithelium. 16S rRNA sequencing data was compared with LN mice with dominant/co-dominant IgA (IgG-IgA-LN; pink) with overlapping features with LN (grey) and/or IgAN (blue).

Results: KM55 staining intensity >0.5 (trace) on a scale of 0-4 discriminates IgAN/IgAV from LN with a sensitivity of 1.00 [0.86-1.00] and specificity of 1.00 [0.82-1.00] (p<0.0001) (Fig 1). KM55 staining with mean 2+ intensity was detected in all SLE patients with LN and no features of LN. IgAN had no difference in KM55 intensity or distribution in non-SLE vs SLE patients. Mesangial KM55 staining was detected in cases with dual LN class V and IgAN. Of 19 IgG-IgA-LN biopsies, 9 (47%) showed positive KM55 staining in the same distribution as IgA.

Conclusions: Our results demonstrate that IF staining of KM55 is valuable in distinguishing IgAN from LN. In SLE patients, negative KM55 staining argues against the presence of IgAN while >0.5 (trace) KM55 staining with dominant/co-dominant IgA staining is suggestive of IgAN as the sole lesion or a co-occurring component of dual glomerulonephritis.

Funding: Other NIH Support - NHLBI [F30HL151138 to BIG]

PO1433

The Significance of Glomerular Galactose-Deficient IgA1 in Patients with Systemic Lupus Erythematosus (SLE)

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Background: Approximately 0.3% of end stage kidney disease in SLE patients is due to non-lupus nephritis. IgA nephropathy (IgAN) is rarely reported in SLE patients. As galactose-deficient IgA1 (Gd-IgA1) plays a key role in the pathogenesis of IgAN but not SLE, the aim was to investigate whether KM55, a Gd-IgA1 specific monoclonal antibody, might identify IgAN in patients with SLE.

Methods: Immunofluorescence (IF) staining of KM55 was performed on 77 native kidney biopsies from 25 non-SLE (IgAN or IgA vasculitis (IgAV)) and 52 SLE patients, the latter including lupus nephritis (LN) with IgG dominant full house staining (LN; n=20), IgAN without features of LN (IgAN; n=11), concurrent LN class V and IgAN (n=2), and LN with dominant/co-dominant IgA (IgG/IgA-LN; n=19). In SLE patients, principal component analysis was carried out on LN, IgAN, and IgG-IgA-LN cases.

Results: KM55 staining intensity >0.5 (trace) on a scale of 0-4 discriminates IgAN/IgAV from LN with a sensitivity of 1.00 [0.86-1.00] and specificity of 1.00 [0.82-1.00] (p<0.0001) (Fig 1). KM55 staining with mean 2+ intensity was detected in all SLE patients with LN and no features of LN. IgAN had no difference in KM55 intensity or distribution in non-SLE vs SLE patients. Mesangial KM55 staining was detected in cases with dual LN class V and IgAN. Of 19 IgG-IgA-LN biopsies, 9 (47%) showed positive KM55 staining in the same distribution as IgA.

Conclusions: Our results demonstrate that IF staining of KM55 is valuable in distinguishing IgAN from LN. In SLE patients, negative KM55 staining argues against the presence of IgAN while >0.5 (trace) KM55 staining with dominant/co-dominant IgA staining is suggestive of IgAN as the sole lesion or a co-occurring component of dual glomerulonephritis.

Funding: Other NIH Support - NHLBI [F30HL151138 to BIG]

PO1434

Tertiary Lymphoid Tissue Development Is Associated with Impaired Renal Function in Lupus Nephritis

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Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE) and the pathophysiology is heterogeneous. Recently, the careful assessment of not only glomerular but tubulointerstitial lesions has been recognized for more precise evaluation of the disease activity, which leads to better management. Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues proposed for more precise evaluation of the disease activity, which leads to better management.

Methods: We examined the presence of TLTs in 205 kidney biopsy samples of patients with LN and investigated the clinical characteristics of patients with renal TLTs. TLTs were defined as organized T and B cell aggregates with sign of proliferation. Histological activity and damage at biopsy were calculated as the National Institute of Health (NIH) activity and chronicity indices (CI).

Conclusions: Murine lupus nephritis is associated with gut dysbiosis, which may contribute to the pathogenesis of nephritis progression. Funding: Government Support - Non-U.S.
Glomerular Diseases: Immunology and Inflammation in Vasculitis and Lupus Nephritis

PO1435

New Drugs and Evolving Treatment Patterns in Lupus Nephritis: How Nephrologists and Rheumatologists Are Responding Differently to New Treatment Options

Background: Existing uptake and experience with recently approved lupus nephritis (LN) drugs belimumab and voclosporin reveal different perceptions, comfort levels, and prescribing intentions between nephrologists and rheumatologists.

Methods: Data were collected over four waves of research between February and May 2021 via online surveys with 50 US nephrologists and 50 US rheumatologists who are actively treating LN patients followed-up with a subset of qualitative interviews.

Results: In a notable trend, rheumatologists deem more of their LN patients as candidates for belimumab, while nephrologists increasingly see their patients as better suited for voclosporin. Rheumatologists tend to rate belimumab higher overall than voclosporin particularly on safety and tolerability, thanks to long term history with the product in SLE patients. Both physician types generally use belimumab as a later-line therapy in mild-to-moderate LN, often to reduce steroid burden. It is generally used with at least one other advanced agent like an antimalarial, steroid, or MMF. Rheumatologists are more likely to use belimumab in moderate-to-severe LN patients given the drug’s perceived quicker onset of action, efficacy, and steroid-sparing effect. Voclosporin is nearly always used concomitantly with advanced drugs like antimalarials, steroids, or MMFs. Rheumatologists appear to be initiating voclosporin most often in CKD Stage 2, while nephrologists are initiating most often in CKD Stage 3. Rheumatologists are the leading prescribers of belimumab, and currently have a slight edge with voclosporin patient initiations as well. Nephrologists are tending to wait longer to initiate, due to cost- and risk-benefit uncertainty compared to other options like tacrolimus. Rheumatologists currently view both drugs as a greater treatment advance than nephrologists; nephrologists believe voclosporin is more of an advance in LN treatment than belimumab.

Conclusions: Physician understanding and comfort level with belimumab and voclosporin MOAs are driving early use and perceptions of the two new LN drugs.

PO1436

Treatment of Crescentic Lupus Nephritis with Voclosporin

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Introduction: Crescent glomerulonephritis (CGN) is a rare complication of Lupus nephritis (LN) and carries a worse prognosis. There is paucity of data regarding effective treatment options for CGN. We present a case of crescentic ANCA negative LN treated with voclosporin (VSN).

Case Description: 19-year-old African American female with 2-year history of Class II LN, treated with hydroxychloroquine 200 mg/day, prednisone 10 mg/day, mycophenolate mofetil 1 gm twice daily and Belimumab, presented with a 2-week history of anasarca and generalized bullous skin rash. On exam BP 126/78 mm Hg, HR 96/min, afebrile, RR 18/min, O2 saturation 97% on room air. Investigations revealed hemoglobin 9.2 g/dl, serum creatinine (SCR) 1.2 mg/dl (baseline 0.6), albumin 1.9 g/dl, hypocomplementemia, microscopic hematuria and proteinuria of 4.3 g. A kidney biopsy showed diffuse crescentic immune complex LN and membranous LN (Figure 1). The patient received IV methylprednisolone 1gm for 3 days, however, became anuric. SCR peaked at 3.5 mg/dl and was commenced on hemodialysis and 7 sessions of plasma exchange. She was started on VSN 15.8 mg BID and after 10 days of therapy, SCR improved and dialysis was discontinued. On discharge, SCR was 2.0 mg/dl and proteinuria 0.9 gm. C4 normalized and C3 improved.

Discussion: There has not been any published case report of Crescentic LN being treated successfully with VSN. Given poor prognostic of CGN, early diagnosis and treatment is imperative. Our patient had rapid recovery of renal function and resolution of proteinuria following treatment with VSN. VSN may be effective in combination with plasma exchange in ANCA negative Crescentic LN. Larger studies with longer follow up are needed to assess the efficacy of VSN in CGN.

Figure. Longitudinal HRU and costs among patients with a5 years of follow-up (N=335)

PO1437


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Background: Lupus nephritis (LN) occurs in ~40% of adults with SLE. Despite the high burden of LN, current care management and utilization data are limited. This retrospective cohort study (GSK Study 214012) used data from the Optum Research Database. Index date was the first claim with a renal diagnosis code indicating LN during the identification period (Aug 1, 2011–Jul 31, 2018). Inclusion criteria: age ≥18 years; ≥2 renal diagnosis codes during the identification period; ≥1 outpatient or ≥2 outpatient SLE diagnosis codes in the 12 months pre index; and continuous enrollment of ≥2 months pre and post index. HRU and costs for the cohort with 5 years of continuous enrollment post index are reported.

Results: Overall, 2159 pts met the study criteria (mean [standard deviation, SD] age, 58.5 [14.9] years; 86.7% female) and 335 had ≥5 years of continuous enrollment post index. HRU and costs were highest in the first year post LN diagnosis (Figure). Mean healthcare costs were $44,205 in Year 1 and ~$30,000/year in Years 2 through 5. Approximately 50% of patients incurred an inpatient stay in Year 1, with ~25% of patients hospitalized in each subsequent year.

Conclusions: Patients with newly diagnosed LN incur substantial HRU and costs, which were highest in the year of diagnosis. These data highlight the need for interventions to prevent renal worsening in SLE.

Funding: Commercial Support - GSK

PO1438

Association of TNIP1 Variants with Disease Severity and Progression and IP-10 Chemokine Levels in Lupus Nephritis Patients

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Background: African American SLE patients experience higher rates of LN, increased progression to ESKD, and higher mortality when compared with white patients, but etiology for this disparity is unclear. We reported that a TNIP1 polymorphism, rs4958881, is a risk variant for lupus nephritis (LN) in African American patients. TNIP1 encodes the protein ABIN1, which negatively regulates the transcription factor NF-κB. We generated mice with an Abin1 knockout (Abin1−/−) and C3aR−/− mice showed no glomerular basement membrane remodeling. D. Trichrome stain with moderate interstitial fibrosis and tubular atrophy (35%).

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Underline represents presenting author.

454
Increased tissue levels of IP-10 have been implicated in pathogenesis and as a diagnostic marker in LN, but the mechanism is unknown. The current project tested a hypothesis that LN severity and enhanced IP-10 levels are associated with the TNPI1 rs4958881 risk allele.

Methods: All endpoints were compared for LN patients w/wo TNPI1 variant rs4958881. Genotype classifications were compared for 125 African American and 133 White American LN patients. Urine and serum IP-10 levels were measured in 33 LN patients using ELISA. Progression of disease was assessed and compared from follow up (mean = 3 yrs) for 33 LN patients. Urine, plasma, and kidney levels of IP-10 were compared for AT1501 (KLH) challenge.

Results: A higher percent of African Americans with Class IV LN had the TNPI1 variant (68%) vs 42% for Whites with Class IV and 93% of African American with Class V LN had the variant versus 38% for Whites with Class V. 26.3% of patients with the variant reached the endpoint of doubling of creatinine or ESKD. Proteinuria at follow up was higher in (2800 mg/g) vs. non-variant (1175 mg/g) patients, suggesting refractory disease in variant patients. There were significantly higher levels of IP-10 in serum and urine from African American versus White LN patients and a trend for association in patients with the variant. Urine and plasma kidney levels of IP-10 were significantly enhanced in ABIN1/D45N versus wildtype mice.

Conclusions: Our findings suggest that TNPI1 variant genotyping and IP-10 measurement could provide precision diagnostics for African American LN patients and that inhibition of NF-κB or neutralization of IP-10 is a promising personalized therapeutic direction for these patients.

Funding: NIDDK Support, Other U.S. Government Support, Clinical Revenue Support

PO1439
Inflammatory Dendritic Cell and Th17 Polarization in Mouse Model of Lupus Nephritis
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Background: We have recently identified inflammatory dendritic cells (iDC) in human lupus kidneys. These cells are over expressed in LN patients compared to healthy controls. Knowledge on how the iDC interact with intra-renal T cells and their role in pathogenesis of LN kidney is crucially needed.

Methods: We examined iDC and T cells in the kidneys of NZM 2410 (NZM), from protein-primed NZM mice (protein-p 300mg/dl) and pre-proteinuric NZM (pre-protein-p NZM) mice by Immunofluorescence (IF). To quantitatively assess iDC and various T cells, we analyzed single cell suspensions obtained by enzymatic digestion followed by gentle MACS dissociation from prot-NZM kidneys and pre-protein-p kidneys by multi-color flow cytometry using specific markers for iDC, CD4+CD45R+ B cells, CD11b, CD11c, CD163, CD11b+, Ly6C+. Interestingly, 2 subtypes of iDCs were identified in NZM mice. FcγR1+/MHCII+CD11b+ and FcγR1+/MHCII-C11b+ and FcγR1-/MHCII+C11b+ and FcγR1-/MHCII-C11b- and differentiated by their presence or absence of CD11c. Flow cytometry analysis of T helper cell phenotypes shows that Th17 expression, but not Th1 expression was significantly upregulated in prot-NZM compared to pre-protein-p NZM in parallel to iDC.

Results: The immunofluorescence studies recapitulated the human LN robust infiltration of the iDC marked by FcγRI in the periglomerular and tubulointerstitium in prot-NZM compared to pre-protein-p NZM. The iDC were also identified to be in close proximity to CD3+ T cells constant with an immunosuppressive analogue. Further characterization by IF revealed iDC in mice LN were FcγRI+, MHCII+, CD163+, CD11b+, Ly6C+. Interestingly, 2 subtypes of iDC were identified in NZM mice, FcγR1+/MHCII+CD11b+ and FcγR1-/MHCII-C11b- and differentiated by the presence or absence of CD11c. Flow cytometry analysis of T helper cell phenotypes shows that Th17 expression, but not Th1 expression was significantly upregulated in prot-NZM compared to pre-protein-p NZM in parallel to iDC.

Conclusions: Similar to human LN, iDC are abundant in prot-NZM LN kidneys compared to pre-protein-p kidneys, and they are clearly seen in the renal interstitium. The presence of CD3+ T cells in LN kidneys; and 3) Th17 cells, but not Th1 cells, correlate with iDC’s expression in LN kidneys. These data suggest that iDC regulate the intra-renal Th17 cell response in LN and contribute to IL-17 mediated kidney injury. Ongoing studies will examine if these iDC are necessary or sufficient for LN pathogenesis.

Funding: Other NIH Support - Department of Internal Medicine MPI grant, The Ohio State University

PO1440
SeqStain Is a Novel, Multiplex Imaging Method for Spatialomic Profiling of Human Kidney Tissues
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Background: Chronic Kidney Disease (CKD) is the ninth leading cause of death in the United States, an emerging global health challenge affecting 10-15% of the population. Lack of reliable biomarkers precludes early diagnosis of CKD. The progression of CKD is known to be dictated by renal tissue changes. For instance in Diabetic Nephropathy, disease progression is accompanied by considerable changes to the glomeruli, reduced podocyte number, inflammation in the renal tissue, influx of immune cells that ultimately lead to tissue damage. Understanding these tissue-centered events on a deeper level is important for effective intervention.

Methods: To understand molecular and cellular composition of tissues and their relative organization in three-dimensional space, we developed a novel multiplex staining method called SeqStain. The SeqStain multiplex platform uses fluorescently labeled DNA oligonucleotides (termed “SeqStain antibodies”) to stain while endolysosomes are used to achieve gentle de-staining after each round. This methodology can fluorescently label primary antibodies, secondary antibodies and Fabs of secondary antibodies to efficiently analyze multiple tissues. We use SeqStain multiplexed with antibodies that would probe different histological regions relevant to the kidney

Results: Normal kidney was stained with SeqStain antibodies and de-stained using endolysosomes. Using SeqStain methodology, we built 20x20-plex panel on kidney tissue and provided a gentle and rapid technique for multiplex imaging. Strikingly, de-staining using the SeqStain method was rapid and removed ~99% of the signal in <1min without affecting tissue integrity. The method was implemented using a simple perfusion setup with readily available components, allowing staining of tens of antigens on a single tissue section. Alignment of images and their analyses provided spatialomic data on multiple cell types in tissue

Conclusions: The SeqStain method offers a gentle, easy-to-use, and effective multiplex imaging technique that provides a unique platform for obtaining spatialomic insights. SeqStain method can profile the CKD kidney tissues and communicate the tissue-centered events that could play a role in disease progression. Currently, we are profiling the CKD tissues in multiplex staining experiments in comparison to healthy kidney to generate spatial maps

Funding: Commercial Support - Eledon Pharmaceuticals

PO1441
A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AT1501
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Background: CD40L is a costimulatory receptor for CD40 found on T helper cells. Binding of CD40L on T cells to CD40 on antigen presenting cells induces downstream immune and inflammatory responses. Inhibition of CD40L signaling can abolish inflammatory responses and prevent the progression of disease, including transplant tolerance. AT-1501 is a humanized anti-CD40L antibody lacking Fc effector function and high affinity binding to CD40L. Purpose: Execute a phase 1 study of AT-1501 to assess safety, pharmacokinetics, and functional activity.

Methods: The study employed a placebo-controlled, sequential, dose-escalation design. 28 healthy subjects and 4 adults with ALS were enrolled. Five sequential ascending doses of AT1501 (0.5, 1, 2, 4, or 8 mg/kg) or placebo were administered by IV infusion. The primary endpoint was the safety and tolerability of AT1501. The secondary endpoint was to determine plasma pharmacokinetics (PK) and anti-drug antibody (ADA) responses to AT1501. An exploratory endpoint was to examine the ability of AT1501 to block an immune challenge in subjects who received a Keyhole Limpet Hemocyanin (KLH) challenge.

Results: Dose proportionality was achieved over the AT-1501 dose range of 0.5 to 8 mg/kg for Cmax and AUC0–∞. The mean AT-1501 t1/2 in healthy volunteers was 16 to 28 days. AT1501 had a safety profile comparable to placebo and was well tolerated in healthy subjects and subjects with ALS. 54% of subjects treated with AT1501 had at least 1 TEAE; 22% of subjects treated with placebo had at least 1 TEAE. The most commonly reported TEAEs overall were headache, somnolence, and upper respiratory tract infection. There were no meaningful laboratory abnormalities, vital sign assessments, ECG assessments, or physical examination findings. Positive ADA responses to AT-1501 were observed in 6 of 30 subjects in the study. There was no dose dependence with respect to the incidence of positive ADA titers. ADA did not appear to affect AT-1501 plasma PK profiles or parameters suggesting they were not neutralizing. 8 mg/kg AT1501 successfully blocked an immune response to KLH challenge in 2 of the 3 subjects tested.

Conclusions: Our results support further clinical development of AT-1501 for transplantation and autoimmune indications.

Funding: Commercial Support - Eledon Pharmaceuticals

PO1442
High Expression of Mincle in Intermediate Monocytes of Patients with Autoimmune Diseases
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Background: Mincle is a transmembrane C-type lectin receptor that is predominantly expressed on macrophages’ surface and regulates innate and adaptive immune and inflammatory responses. Inhibition of CD40L signaling can abolish inflammatory responses and prevent the progression of disease, including transplant tolerance. Thus, playing a pivotal role in tailoring immune response. Mincle’s function associates with its expression levels on immune cells’ surfaces. However, the differential expression of Mincle in various types of immune cells between patients with autoimmune disease and healthy controls (NCs) is yet to be examined, and its clinical relevance remains unclear. Therefore, this study aimed to investigate Mincle expression and distribution in different types of immune cells in patients with AD and NCs, and to explore the clinical relevance and potential mechanisms of Mincle expression levels in immune cells of peripheral blood in patients with systemic lupus erythematosus (SLE).

Methods: Mincle expression levels in leukocyte subtypes and monocyte subsets of peripheral blood from all participants were analyzed using flow cytometry and real time PCR, and the clinical characteristics of patients with SLE were collected for correlation analysis. The intermediate monocytes (IMs) from patients with SLE, healthy NCs, and patients with AD were isolated and stained using specific markers for IMs (CD14+CD11c−), CD16+ T cells, and the differentiations of naïve T cells were detected by flow cytometry.

Results: Mincle was expressed predominantly in myeloid cells, both in peripheral blood and cell lines. Moreover, monocytes expressed higher levels of Mincle than granulocytes in both patients with AD and NCs, and Mincle expression levels were higher in IMs of patients with AD, including patients with SLE, than in those of NCs;
PO1443
Development of Kidney Resident and Recruited Macrophages

Background: Macrophages are part of the phagocyte mononuclear system constantly replaced by the circulating blood monocytes. In the steady state, the myeloid cell compartment is highly heterogeneous, containing various subpopulations. These cells include macrophages and dendritic cells, and each play important roles in tissue maintenance, including development, homeostasis, immunity and repair following tissue injury. The composition of kidney macrophages is not well known.

Methods: A multi-parametric flow cytometry approach was used to identify the resident and recruited macrophage population in the kidneys of male and female C57BL/6J mice aged -7, -21 and -84 days in the steady state. Resident and recruited macrophage populations were characterized based on 33 cell surface and intracellular markers. Both resident and recruited macrophages were identified in the kidneys of male and female mice aged -7, -21 and -84 days in the steady state. We observed two distinct resident macrophage populations in young mice (7 and 21 days old) but by 84-days, male and female mice displayed 4 and 5 resident populations, respectively. The resident macrophage population in 7-day old mice displayed low surface expression of MHC class II and began to shift to an increased expression of MHC class II at 21 days, and high MHC class II expression at 84 days. We detected three recruited macrophage populations in 7- and 21-day-old mice, and two populations by 84-days of age. The recruited macrophage population displayed low MHC class II at all ages in both sexes. Analysis of the global macrophage populations at 84 days of age revealed female mice had twice as many recruited compared to resident macrophages, whereas male mice had an equal distribution.

Conclusions: The data indicate a dynamic change in the kidney macrophage populations with aging and resident macrophage phenotype. The composition of macrophage populations also differs by sex and age. These data suggest each population plays a role in kidney homeostasis. Future studies will be directed towards elucidating the functions of each of the identified macrophage populations.

Funding: NIDDK Support

PO1444
Activation of the Integrated Stress Response Regulates the Production of IL-17 in Tissue Resident Memory T Cells

Background: CD4+ positive T cells produce cytokines and play a central role in immunity. Tissue-resident memory T (Trm) cells remain in organs after infection and contribute to efficient host defense by immediate production of cytokines, such as IL-17A. More recently, it was demonstrated that Trm cells also promote autoimmunity. Therefore, the regulation of cytokine production by Trm cells is of great importance to achieve efficient host defense without excessive inflammation. However, the control mechanisms of cytokine production by Trm cells are not well understood.

Methods: Human and mouse T cells including renal Trm cells were analyzed by single cell RNA sequencing (scRNAseq), polysome profiling combined with bulk RNA sequencing, RT-PCR, flow-cytometry, immunocytochemistry, and mRNA FISH. Mouse models for Staphylococcus aureus infection and crescentic glomerulonephritis were used to induce and study Trm cells in vivo.

Results: Conserved cytokine pathway, polysome profiling and tissue signature analysis of human and mouse tissue samples revealed that resting CD4+ Trm cells in the kidney express IL17A mRNA but do not produce or secrete the cytokine protein without re-stimulation. Mechanistically, we demonstrate that the phosphorylation of eIF2α, a key feature of the integrated stress response (ISR) activation, resulted in recruitment of IL17A mRNA into stress granules, which are organelle crucial for regulating mRNA translation during ISR, thereby inhibiting mRNA translation in resting Trm cells. Finally, we show that re-stimulation of human renal Trm cells through T cell receptor resulted in eIF2α dephosphorylation, leading to efficient translation of IL17A mRNA and subsequent IL17A secretion.

Conclusions: Tissue-resident memory CD4+ T cells in the kidney express high levels of IL-17A cytokine mRNA. Under homeostatic conditions the cytokine mRNA is stored in stress granules. In contrast, these Trm cells rapidly produce IL-17A upon re-stimulation. Our study identifies a novel mechanism of how “poised Trm cells” use the integrated stress response - stress granules pathway to regulate IL-17A cytokine mRNA translation. Dysregulation of this pathway might have a pathogenic role in organ repair and remodeling inflammatory diseases.

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Underline represents presenting author.

PO1445
Differential Cell Cycle and Kinase Activation in IgA1-Producing Cells from IgAN Patients and Healthy Controls Mediated by Cytokine Stimulation
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Background: Some cytokines increase production of galactose-deficient IgA1 (Gd-IgA1) in immortalized IgA1-producing cells derived from peripheral blood of patients with IgAN. Previous work has indicated dysregulated cytokine induced signaling may be responsible, but minimal work investigating the overlapping pathways has been performed. Using single-cell transcriptomics, we analyzed pathway responses in immortalized IgA1-secreting cells derived from IgAN patients and healthy controls (HC) before and after response to a mixture of cytokines.

Methods: A mixture of cytokines mimicking those produced by T-follicular helper (Thh) (IL-4, IL-6, IL-21, CD40L, 50 ng/mL) was used to stimulate immortalized IgA1-producing cells for 30 min before single-cell transcriptomic analysis. Gd-IgA1 level was determined by ELISA. Standard data processing using Seurat was performed along with Alteryx for IgA1 separation. Differential markers for genes in unstimulated and stimulated conditions were analyzed for pathway differences using the GSEA MSig database, and kinase-transcription factors were imputed using X2CK analysis.

Results: Thh cytokines mediated overproduction of Gd-IgA1 in IgAN cells but not HC. IgA1-secreting subpopulations were separated, and UMAP was used for unsupervised dimension reduction analysis. Within these UMAP groups, pathway analysis found multiple significant associations, including down-regulation of cell cycle processes (FDR<1X10^-25) in IgAN IgA1 cells compared to an increase in HC (FDR<4.7X10^-25) cells after Thh cytokine stimulation. Analysis of imputed kinases changed in IgAN stimulated IgA1 cells compared to HC identified MAPK14 (p=1X10^-28 and AKT1 (p<1X10^-28), which have been associated with controlling O-glycosylation expression. Conclusion: Significant changes in imputed kinases previously associated with O-glycosylation were found in IgA1-secreting cells in IgAN compared to HC in response to Thh cytokine stimulation. When stimulated with cytokines, there were significant decreases in cell cycle and proliferation pathway responses in the IgA1-secreting cells from IgAN vs. HC samples. Further investigation is needed to determine the role of cell cycle and MAPK14 pathways in driving Gd-IgA1 overproduction mediated by cytokine stimulation.

Funding: NIDDK Support

PO1446
Serum and Glomerular Complement Component as Biomarkers in the First South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort (GRACE-IgAN)
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Background: The Glomerular Research And Clinical Experimental-IgA Nephropathy in Indians is a prospective longitudinal cohort. The study protocol has been published and is registered with WHO trial id: ISRCTN36831459. The role of serum and glomerular complement components in South Asian IgAN is unknown.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 192 (97%) patients completed 3 years. Serum complement C3 and C4 levels and glomerular C3d, C4d and C5b-9 by IHC were quantified at baseline in IgAN patients. Composite outcome (CO) was defined as a ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m^2 or RRT/death.

Results: 195 patients (97%) completed 3 year longitudinal follow-up. Lower serum C3 was significantly associated with S1, T1/T2 according to the Oxford MEST grading and with global glomerulosclerosis (GS-33%) whereas higher C4 levels were associated S1 scores. Increased mesangial C3d deposition correlated with increased mean arterial pressure, proteinuria, decreased serum albumin, decreased eGFR and with GS-33%. Increased C4d, increased mesangial C4d correlated with increased systemic blood pressure, decreased serum protein and decreased eGFR and with GS-33%. Mesangial deposition of C5b-9 did not have any clinical associations. Lower serum C3, higher serum C4 and increased mesangial C3d was significantly associated with CO over three years.

Conclusions: Serum and tissue complements could be potential biomarkers for severity and progression in the GRACE-IgAN cohort. This requires further validation.

Funding: Government Support - Non-U.S.
PO1447

Immune Complexes Containing Galactose-Deficient IgA1 Deposit on Mesangium Through Damage to Endothelial Cells

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Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). However, the pathogenic role of mesangial Gd-IgA1-containing immune complexes (ICs) remains unclear. The endothelial surface glycocalyx modulates microvascular function. Loss of the glomerular endothelial glycocalyx is known to be involved in albuminuria. Here, we examined whether the deposition of Gd-IgA1-containing ICs in the mesangium may lead glomerular endothelial cell dysfunction in this disease.

Methods: Gd-IgA1 and recombinant anti-glycan IgG were used to form ICs to inject into nude mice. The renal microvascular endothelial glycocalyx removal of the injected nude mice was evaluated by real-time glycocalyx imaging. Human renal glomerular endothelial cells (HRGECs) were used to assess the potential capacity of Gd-IgA1-containing ICs to activate endothelial cells.

Results: After co-culture of Gd-IgA1-containing ICs with HRGECs, mRNA expression levels of endothelial adhesion molecules (ICAM-1, VCAM-1 and E-selectin) were significantly upregulated (P<0.01). Expression levels of proinflammatory mediators (TNFα and IL-6) that are able to induce the expression of the adhesion molecules on endothelial cells were also increased (P<0.001). Nude mice injected with Gd-IgA1-containing ICs showed podocyte and endothelial injuries with IgA, IgG, and C3 co-deposition along the glomerular capillaries and in the mesangium. Moreover, albuminuria and hematuria were also induced. Real-time glycocalyx imaging showed that renal microvascular glycocalyx was decreased immediately after the injection of Gd-IgA1-containing ICs and then mesangial IgA deposition was increased.

Conclusions: Present data suggest that Gd-IgA1-containing ICs may induce glomerular endothelial injuries resulting in mesangial deposits.

PO1448

Immune Complexes in the Peripheral Blood of Patients with IgA Nephropathy Contain Polymeric Galactose-Deficient IgA1 Associated with IgG and Complement C3

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein immune complexes (IC) consisting of IgA1 with some hinge-region O-glycans deficient in galactose (Gd-IgA1) and IgG autoantibodies deposit in the kidneys and induce injury. Although the glomerular immunodeposits are enriched for Gd-IgA1, not much is known about the distribution of different molecular forms of Gd-IgA1 in circulation.

Methods: Total serum IgA1 was isolated from 7 Caucasian and 10 African American patients with IgAN by jaccalin-affinity chromatography. Different molecular forms of IgA1 were then separated by size-exclusion chromatography (SEC). Gd-IgA1 was detected by lectin ELISA. IgA1-IC were isolated by SEC from sera of 4 IgAN patients. Biological activity of the isolated IC was assessed measuring the proliferation of cultured primary human mesangial cells (MC). IgA1, IgG, and complement C3 were analyzed by SDS-PAGE/immunoblotting.

Results: Total serum IgA1 included monomeric and polymeric forms and IgA1 bound in IC. Monomeric IgA1 represented ~88-92% of total IgA1, whereas polymeric IgA1 represented ~8-12%. IgA1 in IC was the least abundant form, representing <0.4% of total IgA1. Relative representation of Gd-IgA1 was highest in IC, followed by polymeric forms, and lowest in monomeric forms. Gd-IgA1 in IC had minimally sialylated O-glycans, whereas polymeric and monomeric forms were substantially sialylated. Caucasian patients had higher content of Gd-IgA1 in polymeric and monomeric forms of IgA1 compared to those of African American patients (P<0.03 and P<0.005, respectively). IgA1-IC in sera of IgAN patients had molecular mass ~700 kDa and stimulated proliferation of MC. These IC consisted of polymeric IgA1, IgG, and complement C3.

Conclusions: Biologically active IC in the circulation of IgAN patients contain polymeric, minimally sialylated Gd-IgA1 associated with IgG and C3. These findings support the pathogenic role of Gd-IgA1-IgG IC in IgAN.

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PO1451

Histopathologic Association of Lambda Light Chain Predominance in IgA Nephropathy
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Background: A relative predominance of lambda (λ) over kappa (κ) light chain deposition has long been recognized in IgA Nephropathy (IgAN), which is not unique to any other glomerular disease. The reason for this predominance is unknown but may be related to a purported predominance of λ chain expression by gut associated lymphoid tissue B cells. There is limited information regarding the histopathologic findings, if any, associated with predominant λ light chain deposition. Utilizing the CureGN IgAN cohort, we evaluated if predominant λ chain deposition was associated with histologic markers of disease activity by examining MEST characteristics and other variables.

Methods: We divided the CureGN IgAN cohort into two groups based on the intensity of light chain deposition by immunofluorescence. The λ dominant group (LD) was defined by a difference in intensity score of staining of λ minus κ ≥ 1+, and the λ-κ codominant group (KL) by a difference of λ minus κ ≤ 1+. Fisher’s exact test was used to compare the histopathologic changes between the groups with respect to M, E, S, T, scores, total crescents, percent (% of globally sclerotic glomeruli, % of glomeruli with fibrinoid necrosis, degree of interstitial inflammation, and the intensity of IgG, C1q, and C3 staining.

Results: Among 695 IgAN patients, the kidney biopsy digital images of 269 patients were reviewed by CureGN pathologists and 234 patients had reported λ and κ staining intensity. Of these, 96 (41%) patients were classified as LD (including 7 patients (3%) with λ, monotypic staining) and 138 (59%) classified as KL. The two groups did not differ significantly in age, sex, or race. Compared to the KL group, the LD group had a greater frequency of endocapillary hypercellularity (E1, 51.1% vs 36.3%, p=0.04) and IgG staining intensity ≥ 1+ (37.3% vs 21.9% p=0.01). There were no significant differences between groups with respect to any other histologic finding.

Conclusions: In IgAN, patients with predominantly λ mesangial deposition are more likely to have increased endocapillary hypercellularity and IgG deposition, two findings previously linked with greater histologic disease activity and possibly worse prognosis. Further studies are needed to elucidate if the predominance of λ chains represents a unique pathogenesis in a subset of patients, or if it imparts a more severe disease course.

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PO1450

Structural Characterization of Autoreactive IgG Antibodies in the Context of IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most prevalent glomerulonephritis in the world. The pathology of IgAN is characterized by deposition of immune complexes in the kidneys. These complexes can trigger inflammation and mesangial cell proliferation in patients, where up to 40% of cases progress to renal failure. The pathogenic immunodeposits in kidneys of IgAN patients have been shown to contain IgA1, which has O-linked glycans in the hinge region of the heavy chain that are deficient in galactose (galactose-deficient IgA1; Gd-IgA1) and IgG autoantibodies to Gd-IgA1. Sequencing of IgG heavy chain variable regions from IgAN patients has identified a correlation between a serine residue, introduced by somatic hypermutation into the framework leading into the third hypervariable loop of the heavy chain, with an increased association of IgG autoantibodies with Gd-IgA1. We set out to understand how this single amino acid mutation affects the Ig Fab structure and antigen recognition with the aid of protein cryo-cryo-electron microscopy, reverse engineering, and binding studies.

Methods: Recombinant IgG constructs (rIgG) based on IgAN patient sample sequences and site-specific mutants were expressed in 293F cells and purified. Fab s were cleaved from IgG, purified, crystallized, and their protein structures determined. Binding differences between Gd-IgA1 and intact rIgGs were determined with ELISA-based experiments.

Results: Comparisons of rIgF Fab structures derived from a healthy control patient and an IgAN patient showed conformational differences that possibly influence the recognition of Gd-IgA1. Using this structural data and bioinformatics to guide antibody design, we reverse engineered the IgG from a healthy patient control to modulate binding to Gd-IgA1. Site-directed mutagenesis and binding studies indicated that residues in our designed, we reverse engineered the IgG from a healthy patient control to modulate binding to Gd-IgA1, and we have further identified residues in the Fabs that are important for Gd-IgA1-binding. This knowledge could inform future strategies to inhibit pathogenic immune complex formation.

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458
Glomerular Diseases: Immunology and Inflammation in IgANP, C3GP, TMA, and Nephrotic Diseases

Methods: Plasma and urine levels of complement proteins (C4c, C3b and soluble C5b-9) were measured using in-house sandwich-ELISAs. Treatment differences between baseline, end of treatment and end of study were assessed by mixed-effects model analysis. The effect of the treatment correcting for the baseline was assessed by multiple linear regression. Significance: p < 0.05. Urinary protein excretion was adjusted for creatinine excretion.

Results: Circulating levels of MASP-3 were decreased in a dose-dependent manner after treatment (p = 0.013 Nefecon 8 mg/day, p = 0.0080 Nefecon 16 mg/day). MBL- creatinine was significantly reduced in the urine by both doses of Nefecon compared with placebo (p = 0.0001 Nefecon 8 mg and 16 mg/day). CL-11-creatinine levels were also significantly reduced in a dose-dependent manner after Nefecon administration (p = 0.0411 Nefecon 8 mg/day, p = 0.0095 Nefecon 16 mg/day). Complement activation markers and ficolin-3 levels were detectable in urine but levels remained unaltered.

Conclusions: Treatment with Nefecon modulates components of both the alternative (MASP-3) and lectin (MBL- and CL-11) pathways of complement, two pathways known to be important in mediating kidney damage in IgAN. These initial observations warrant further investigation.

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POI455

Defining Cell Type Specificity of TNF Targets in Nephrotic Syndrome

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Background: Mechanistic, targeted therapies are needed for patients with FSGS and MCD, as diverse biological processes produce similar histologic injury patterns. Bulk transcriptomic data from kidney biopsy tissue can be used to find subgroups with shared molecular features, but cellular signaling networks need to be defined.

Methods: Consensus clusters were enriched against bulk RNA sequencing data from the tubulointerstitial (TI) compartment of 220 participants from the NEPTUNE cohort, a study of children and adults with nephrotic syndrome enrolled at the time of kidney biopsy. Clusters were assessed for association with clinical outcome. Differential gene expression analysis was analyzed for enrichment of canonical pathways and functional groups between patient clusters. Nuclei were extracted from renal biopsies, processed, and quality control analyzed to remove low quality nuclei. Nuclei identity were assigned by comparisons of enriched genes in a cluster to previously identified cell-type specific genes.

Results: One cluster of 59 patients was associated with a greater risk of loss of kidney function over time and observed TNF activation. To test the cellular source of the TNF pathway biomarker candidates, we performed mRNA-seq on 10 NEPTUNE biopsies, 5 with high TNF activity scores and 5 with moderate to low TNF activity scores in TI gene expression profiles. We pooled 45,175 nuclei into 15 clusters, which included all major kidney cell types. TNF expression was found in nuclei from immune clusters and in a proximal tubule and loop of Henle clusters. TNFRSF1A was universally expressed across all clusters, while TNFRSF1B was universally expressed across cell clusters, while TNFRSF1B showed more restrictive expression. TNF targets CCL2 and TNF superfamily - higher levels in all patients with activated TNF scores with maximal increase in epithelial cells (proximal and podocytes). Kidney organoids confirmed MCP1 (encoded by CCL2) and TIMP1 upregulation by TNF treatment.

Conclusions: TNF, TNF receptors, and TNF-responsive biomarkers reflect alterations in inflammatory and intrinsic kidney cell populations in patients with TNF-associated signaling profile and are currently assessed as TNF target engagement biomarkers in a clinical trial of FSGS patients (NCT04009668).

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases Research; National Center for Advancing Translational Sciences, Private Foundation Support
POI457
Dysregulated T Cell Metabolomic Profile in Patients with Steroid-Resistant Nephrotic Syndrome

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**Background:** We have recently reported early relapse following rituximab in patients with minimal change disease was associated with baseline reduction in regulatory T-cells and T-cell hyporesponsiveness to activation, suggesting chronic T-cell activation. This study aimed to compare T-cell activation and characterise the metabolic alterations associated with T-cell hyporesponsiveness in patients with steroid-dependent (SDNS) and steroid-resistant nephrotic syndrome (SRNS) in relapse.

**Methods:** A total of 48 patients with childhood-onset SDNS (n=31) and SRNS (n=17) were recruited during relapse. T-cell activation assay was performed on whole blood while metabolomic profiling was performed on purified stimulated CD4 T-cell culture supernatants (n=23) using GC-MS/MS and analysed using Shimadzu Smart Metabolites Database. Differences in the metabolomic profile between SDNS and SRNS were identified using PLS-DA (SIMCA), and pathway analysis was performed using MetaboAnalyst 4.0. Metabolomic validation assay was performed using Glucose 6 Phosphate Dehydrogenase (G6PD) assay kit.

**Results:** SRNS patients had significantly lower T-cell expression of CD69 (88a.3% vs 91a.3%, P=0.024) and IFNγ (1.19a.73% vs 6.6a.133%, P=0.016) compared to SDNS patients. PLS-DA modeling of the 93 metabolites identified in CD4 culture supernatants yielded one fitted component, in which 24% of the variability in metabolites measured (R²X) could explain 58% of the variation in steroid-response (R²Y). Of note, 85% of the metabolites tended to be lower in SRNS compared to SDNS patients. Pathway analysis of the 38 metabolites with VIP>1 implicated the biosynthetic pathways glyoxylate and dicarboxylate metabolism, ascorbate and aldarate metabolism as well as galactose metabolism (Benjamini-Hochberg P<0.05). Interestingly, the 2 metabolites with the highest VIP score have been implicated as downstream products in the pentose phosphate shunt and were reduced in SRNS compared to SDNS patients (P<0.001). G6PD activities in SDNS patients in relapse negatively correlated with T-cell expression of CD69 (r=-0.58, P=0.047).

**Conclusions:** We demonstrated that muted T-cells response to in vitro stimulation in SRNS patients was associated with metabolic quiescence, with dysregulated biosynthetic pathways including the pentose phosphate shunt.

**Funding:** Government Support - Non-U.S.

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POI458
Blocking the IL-1β/IL-1Ra Signaling as a Potential Therapy for Multidrug-Resistant Nephrotic Syndrome

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**Introduction:** Idiopathic nephrotic syndrome (NS), Steroid-resistant patients with complete or partial resistance to the combination of prednisone and steroid sparing-agents are at high risk to progress to end-stage kidney disease. Considering the toxicities associated with chronic use of these drugs, alternative interventions are urgently needed. IL-1β/IL-1Ra has been recently suggested as a possible mechanism of complement-mediated progression of Focal Segmental Glomerulosclerosis.

**Case Description:** A 26-year-old white woman had FSGS (kidney biopsy) presenting with NS and kidney failure. Serum creatinine level was 1.6 mg/dL, urinoma protein excretion 20.4 g/d and serum albumin 0.9 g/dL. She received methylprednisolone, 1g rituximab, and CNI with partial remission. Three months later, she presented relapse of NS and kidney failure requiring 5 HD: CNI was switched to MMF. Immunoglobulins rituximab, and CNI with partial remission. Three months later, she presented relapse of NS and kidney failure requiring 5 HD: CNI was switched to MMF. Immunoglobulins rituximab, and CNI with partial remission. Three months later, she presented relapse of NS and kidney failure requiring 5 HD: CNI was switched to MMF. We hypothesized that the pathogenesis of minimal change disease (MCD) may be associated with mitochondrial injury and that the degree of mitochondrial injury at the time of diagnosis may serve as a prognostic marker in MCD.

**Methods:** We retrospectively enrolled patients with MCD who were followed up for more than 5 years and IgA nephropathy (IgAN) patients as controls (n = 20 each). Focusing on the stimulator of interferon genes (STING) pathway activated by mitochondrial injury, immunohistochemical (IHC) staining for STING was performed on kidney tissue at the time of diagnosis. The IHC stain site and signal intensity for STING were analyzed. Time-averaged proteinuria (TA-proteinuria) was calculated as the average of the mean of proteinuria measurements were obtained by 24-hour urine collection every 6 months for each patient. A relapse after treatment was defined as proteinuria >3.5 g per 24 hours or complete or partial remission.

**Results:** In patients with IgAN and MCD, kidney tissue from 13 patients each showed positive IHC staining for STING. While various kidney structures including glomeruli and tubulointerstitium were stained in IgAN patients, the glomerulus was exclusively stained in MCD patients (Figure). MCD patients were divided into the high (n = 6) and low (n = 14) intensity subgroups according to the signal intensity based on 2+ and more or less, respectively. TA-proteinuria and frequency of relapses during the follow-up period were higher in the high intensity group than in the low intensity group (1.18 ± 0.54 vs. 0.57 ± 0.45 g/d, p = 0.022; and 0.72 ± 0.60 vs. 0.09 ± 0.22 episodes/year, p = 0.022, respectively).

**Conclusions:** These findings suggest that more severe mitochondrial injury, as represented by a high signal intensity of IHC stain for STING at the time of diagnosis, could be used as a prognostic marker to predict poor prognosis in MCD.

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POI460
Maturation of Decay Accelerating Activity Response Across the Natural History of C3 Glomerulopathy

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**Background:** C3 glomerulopathy (C3G) is an ultra-rare complement-mediated renal disease characterized by dysregulation of the alternative pathway (AP) of complement. Dysregulation is often driven by a nephritic factor (C3NeF), an autoantibody to the C3 convertase (C3BbBb) of the AP. We hypothesized that the properties of Nef change
over time and that changes will be associated with changes in underlying complement dysregulation.

**Methods:** IgG was purified from normal human serum and from sera collected across six time points of a well characterized C3G patient. Using SPR (Biacore), the C3 convertase (C3bBb) was formed on a CM5 sensor chip. Purified test or control IgG was injected to form the Neu-C3NfBb complex. The ability of native complement regulators to decay the Neu-C3NfBb complex was assessed by injecting Decay Accelerating Factor (DAF), Complement Receptor 1 (CR1), Factor H (FH), or control reagent. Residual C3bBb was determined by the ratio of post- to pre-regulated convertase. Data were compared to time-matched complement biomarker results.

**Results:** The presence of Neu conferred resistance to the normal decay accelerating activity (DAA) by DAF, CR1, and FH. Resistance to DAA was highest in the earliest sample (S1, p = 0.0001), with a reduction in subsequent samples. This change was independent of Neu titer and coincident with reduced complement activity. Low DAF resistance was maintained in later samples, whereas CR1 and FH resistance gradually increased.

**Conclusions:** Neu-stabilized C3bBb resistance to native DAA proteins matures over time and is independent of Neu titer. Changes in response to regulators is accompanied by a relative change in underlying complement dysregulation as reflected by complement biomarkers. How this variance (in time and across regulators) impacts disease course and outcome in patients with C3G or whether the phenomenon represents a novel treatment target warrants further study.

**Funding:** NIDDK Support

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**POI146**

C3 Glomerulonephritis with Nephritic Factor Treated with Rituximab

**Case Description:** Patient is a 64-year-old male diagnosed with biopsy proven C3GN after being found with decreased kidney function with a peak creatinine of 1.97 mg/dL and nephrotic range proteinuria with a maximal urinary protein excretion of 4.3 g/dL. Evaluation revealed low C3 and C4 at 60 mg/dL and 5 mg/dL respectively, negative monoclonal testing, and a C3NeF of 21 unit/mL (reference range 0). Patient was initiated on prednisone 60 mg/day with taper, MMF with a maximal dose 3 grams/day, and valacyclovir for 2 years with little improvement in clinical parameters. Therapy was switched to rituximab 1 gram on weeks 0, 2, 6. Within 3 months patient had; normalization of complements, negative C3NeF, 0.7 urine protein-to-creatinine ratio (UPCR), and serum creatinine 1.5 mg/dL. Since his initial rituximab regimen 2 years ago, he remains off maintenance therapy, with negative C3NeF, normal complements, 0.1 UPCR, and serum creatinine 1.04 mg/dL.

**Discussion:** C3GN was successfully treated with rituximab based on the disappearance of C3NeF and improvement in clinical parameters. Rituximab was chosen to target CD20 cells to halt the production of the C3NeF autoantibody. Laboratory response (complements and C3NeF) was seen within 3 months of initial rituximab dosing, and UPCR and serum creatinine required a longer follow up for a nadir. Recurrence of relapse is being monitored using serial C3NeF measurements. We believe that targeted B cell therapy should be considered in the treatment of C3GN cases which are C3NeF antibody mediated.

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**POI1462**

Complement-Activated Polymorphonuclear Neutrophils Contribute to C3G Pathogenesis

**Background:** C3G is caused by dysregulation of the complement alternative pathway, but there is a gap in the pathogenetic cascade from complement activation (intravascular space) to inflammation and complement deposition in the glomeruli (extravascular space). Recently, biopsies have shown the presence of (activated) polymorphonuclear neutrophils (PMNs) in C3G glomeruli indicating an underappreciated role for PMNs in C3G pathogenesis.

**Methods:** PMNs were investigated in a transwell chamber allowing for different environments. Conditions were chosen to resemble the intravascular space (top well; serum containing) versus extravascular space (bottom well; serum-free conditions). PMNs were stimulated in the top well via various agonists, including complement, and allowed to transmigrate to the bottom well where they were monitored for the formation of Neutrophil Extracellular Traps (NETs) via immunofluorescence and SYTOX assay. Circulating C3G patient PMNs were examined for priming via flow cytometry.

**Results:** Upon complement stimulation, PMNs showed evidence for priming in serum conditions (top well). PMNs travelled to the bottom well following chemotractant fMLP where they then completed the process of NET formation (NETosis) in serum-free conditions (bottom well). Results were validated ex vivo using C3G patient PMNs and autologous serum (Figure). In addition, incubation of control PMNs in C3G patient serum revealed a correlation between serum-albumin levels and the degree of NET formation. C3G patient PMNs showed upregulation of CD11b compared to controls.

**Conclusions:** Assigning a pathogenetic role to PMNs in C3G identifies a new treatment and monitoring strategy with the potential for improved long-term outcomes and quality of life.

PMNs were seeded in the top well of a transwell system and allowed to transmigrate for 12 h. PMNs from both wells were stained for IF with DAPI (blue), Citrullinated histone 3 (Ch3H3; green) and Myeloperoxidase (MPO; red). Scale bar 20 um. 63x magnification.

**POI1463**

Differential Expression of Complement and Non-Complement Proteins in C3 Glomerulonephritis and Dense Deposit Disease

**Background:** C3 glomerulopathy comprising dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) results from overactivation of the alternative pathway of complement. Mass spectrometry (MS) studies have previously shown accumulation of complement proteins in C3GN and DDD. However, complete MS analysis of non-complement proteins and comparison of complement proteins in C3GN and DDD has not been done.

**Methods:** We performed laser microdissection of glomeruli followed by MS in 12 cases each of biopsy-proven C3GN and DDD, and 6 control cases of time 0 transplant biopsies.

**Results:** Compared to the controls, C3GN showed increased intensity based absolute quantification (iBAQ) values of C3 (20-fold), C5 (52-fold), C7 (90-fold), C8 (66-fold), C9 (30-fold), C1r/C1s (146-fold) and CFR3 (65-fold). Similarly, DDD showed also increased iBAQ values compared to controls of C3 (26-fold), C5 (365-fold), C6 (473-fold), C7 (261-fold), C8 (353-fold), C9 (159-fold), and CFHR1 (73-fold). When DDD was compared to C3GN, there was a 2-5 fold increase in iBAQ values in C5, C7, C8, C9 and C9 (p<0.001), although there was no significant difference in C3. Among the non-complement proteins Apolipoprotein E (APOE) and A-II and V (APOA-II and V), Serine protease HTRA1, Rykandine receptor 1 (RVR1), and Translational activator GCN1 were expressed 3-7 fold higher in DDD compared to C3GN (p<0.001). On the other hand, proteoglycan 2 and 3 (PRG2 and 3), angiostatin (AGT) and properdin (CFP) were expressed 2-5 fold higher in C3GN compared to DDD (p<0.001).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: MS of C3GN and DDD show high iBAQ values of complement proteins. DDD shows a higher iBAQ values in terminal complement proteins compared to C3GN. In addition, proteins such as APOE and APOA I/FV are increased in DDD compared to C3GN, while PRG2/3 and properdin are increased in C3GN compared to DDD suggesting a role for the proteins in the pathophysiology of C3GN and DDD.

PO1464
Clinical and Histological Features of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: A Single-Center Retrospective Study from China
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Background: PGNMID is a new entity of monoclonal gammopathy affecting the kidney characterized by intact monoclonal immunoglobulins (mlg) deposits that result in membranoproliferative pattern of glomerular injury. In this study, clinical and histological of PGNMID cases were evaluated.

Methods: A total of 23 patients with biopsy-confirmed PGNMID in native kidney diagnosed between December 2015 to April 2021 were enrolled in this study. Clinical, histological, hematologic, and follow-up data were abstracted from the medical record.

Results: Of 23 cases, majority were male (65.2%), and the mean age was 49.5 years with 8 cases (34.8%) under 40 years old. At the time of biopsy, 19 cases had proteinuria with a mean 24h urine protein of 3.99g (0.28 to 8.96), 11 of 22 cases had nephrotic syndrome, and 18 of 22 cases had hematuria. The mean serum creatinine was 1.52mg/dl (0.6 to 7.8), 15 cases (65.2%) had eGFR<90 mL/min (CKD-EPI), and 4 cases had eGFR <60 mL/min. Eleven of 23 cases (47.8%) showed MPGA, 6 cases showed EPGN, 2 cases showed MesPGN, and 2 cases showed MN. By IF, 21 cases (91.3%) showed mIgG deposits (12 IgG3, 5 IgG1, 1 IgG1A, 1 IgG3, and 2 IgGk without determined subclass) and 2 cases (8.7%) showed mIgA deposits. All cases showed C3 co-deposits, and 6 of 18 cases (33.3%) had a low serum C3 level. EM revealed unorganized and granular deposits in the mesangial area (17 of 17), subendothelial area (15 of 17), and subepithelial area (12 of 17). Three of 4 cases whose eGFR<60 mL/min showed EPGN. SIFE showed mlg that matched the renal deposits in 2 of 13 cases (15.3%). After mean follow up of 3 months in 3 cases, 1 patient treated with bortezomib+CTX+DXM and another patient treated with rituximab both achieved partial renal remission. But the third patient treated with rituximab had a persistent renal dysfunction. Of note, previous or concurrent infections by fungi, HIV, HBV, HPV or other undetermined pathogen, were observed in 5 cases (21.7%). We also found 1 patient with autoimmunity and another with malignancy.

Conclusions: Compared with previous reports, our PGNMID cases showed similar clinical and histological features. EPGN pattern seems to be associated with more severe renal function damage. Previous or concurrent infections, autoimmunity and malignancy were observed in 21.7% of cases.

PO1465
Diagnostic and Risk Factors for Deregulated Complement in Thrombotic Microangiopathy
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Background: The syndromes of thrombotic microangiopathy (TMA) are diverse and represent severe endothelial damage caused by various etiologies. The early recognition of complement-mediated (C-TMA) is of utmost importance to select patients for complement inhibition. Whether or not clinicopathologic features at presentation can distinguish C-TMA from secondary TMA and/or predict the response to complement inhibition remains unknown.

Methods: Fifty-seven patients with TMA on kidney biopsy and a normal activity of von Willebrand factor cleaving protease were screened for deregulated complement using ex vivo C5b9 formation on the endothelium and genotyping. Massive ex vivo C5b9 formation and/or rare complement gene variants defined C-TMA. Clinicopathologic features that may distinguish C-TMA from secondary TMA were studied. Regression models were used to assess the prognostic value of chronic damage on kidney biopsy.

Results: C-TMA was diagnosed in 30 patients (coexisting conditions, n=26 [87%]), including 16 (53%) cases with rare complement gene variants; 27 patients had secondary TMA related to autoimmunity (n=13), hypertension (n=10), and other etiologies (n=4). Patients presented with acute kidney injury, while systemic hemolysis was uncommon in both groups (n=14/30 vs. n=6/27; P>0.05). C-TMA was linked to younger age (37 [14] vs. 46 [15] years; P=0.04), low plasma C3 (n=16/29 vs. n=3/22; P=0.01), and glomerular thrombosis (n=19/30 vs. n=8/27; P=0.02) as compared to secondary TMA; glomerular thrombosis, however, was common in patients with autoimmunity (n=6/13; P=0.05 vs. C-TMA). These characteristics, when combined, had a specificity and sensitivity for C-TMA of 100% and 33%, respectively. Eculizumab treatment was associated with clinical remission in C-TMA (n=12/14; P<0.01 vs. n=3/16 untreated patients). Morphologic features of chronic damage, i.e., glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis, did not predict prognosis; 5 out of 6 patients with C-TMA and moderate-to-severe chronicity scores treated with eculizumab recovered and/or improved kidney function.

Conclusions: Patients with TMA, low plasma C3, and glomerular thrombosis who present at younger age (i.e., <45 years) are at high risk for C-TMA. Although a kidney biopsy is often needed to detect the TMA, morphologic features of chronic damage cannot predict prognosis.
Hematopoietic Stem Cell Transplant Membranous Nephropathy Is Associated with Protocaderhin FAT1
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Background: Membranous nephropathy (MN) is a common cause of proteinuria in patients with a hematopoietic stem cell transplant (HSCT). The antigen(s) responsible for MN in HSCT-associated MN is unknown.

Methods: We performed laser microdissection and mass spectrometry (MS/MS) of glomeruli of 230 cases of PLA2R-negative MN to detect novel proteins/antigens in MN. These included PLA2R-negative MN developing in the setting of HSCT and de-novo MN in the kidney transplant.

Results: We detected a novel protein Protocaderhin FAT1 (FAT1) in 9 cases of PLA2R-negative MN. Of the 9 FAT1-associated MN cases, 7 patients followed HSCT and 2 followed kidney transplant (de-novo MN). HSCT was done for treatment of AML (5 cases), MDS (1 case) and essential thrombocytopenia (1 case). All 9 cases were negative for known antigens of MN including PLA2R, THSD7A, NELL1, PCDH7, NCAM1, SEMA3B and HTRA1. Baseline PLA2R spectral counts were detected in 7 of the 9 cases. The FAT1 total spectral counts ranged from 27 to 70 (mean 44 ± 13.1). FAT1 was not detected by MS/MS in 115 control cases that included time 0 transplant, minimal change disease, FSGS, diabetes and IgA nephropathy. FAT1 was also not detected in 28 cases of PLA2R-positive MN. No case of FAT1-associated MN was detected in a non-transplant setting. The mean age of patients with FAT1-associated MN was 56 ± 9.7 years, 7 patients were females and 2 were males. MN occurred 2.5 ± 0.8 years and 7.5 ± 1.2 years after HSCT and kidney transplant, respectively. The mean serum creatinine and proteinuria at kidney biopsy was 1.9 ± 1.2 mg/dL and 7.4 ± 5.4 gms/L, respectively. Kidney biopsy showed IgG (2-3+), and minimal C3 (0-1+) along glomerular capillary walls; electron microscopy showed stage II MN in 8 out of 9 cases.

Conclusions: FAT1 appears to be a unique protein found in MN developing in the setting of HSCT and de-novo MN following kidney transplant. Further studies to localize FAT1 on the glomerular basement membranes and detect circulating antibodies are ongoing.

POI1468
Netrin G1 Is a Novel Target Antigen in Membranous Nephropathy

Background: PLA-R is the main target antigen in membranous nephropathy (MN) representing 70-80% of cases. In the past years a number of confirmed, or potential target antigens, such as THSD7A, NELL1, HTRA1, SEMA3B and PCDH7 have been reported, showing that the pathophysiology of PLA2R-antibody (ab) negative MN represents a diverse repertoire of antigens with low frequency.

Methods: Western blot (WB) analysis was used to identify sera of MN patients with IgG4 specific signals binding to antigens in the membrane fraction of human glomerular extracts (HGE). Only sera which were negative for PLA-R- and THSD7A- were used. IgG4-Ab from the serum of an index patient was purified and used to immunoprecipitate the corresponding target antigen from the membrane fraction of HGE. The purified antigen in the eluate was identified by mass spectrometry. Recombinant protein was used to confirm the reactivity of patient sera by WB and identify other patients in a large cohort of MN patients. The deposition of the target antigen in the glomerular immune deposits was confirmed by immunohistochemistry (IHC).

Results: Using this approach, we identified Netrin G1 (NTNG1) as a novel target antigen in MN. NTNG1 is a 50 kDa secreted glycoprotein, which is attached to the cell surface by a GPI anchor (Fig. A, B). We identified NTNG1-ab in two out of 110 PLA-R- and THSD7A-ab negative MN patients. A follow-up of 5 years was available for the index patient. During this time, both proteinuria and NTNG1-ab persisted while renal function (eGFR 73 ml/min) and hypoalbuminemia (2.89 g/dl); 24h proteinuria was 3.6 g/24h. Autoantibodies (ANA, ENA, DNA, LAC, anti-cardiolipin, ANCA) were undetectable, serum immunoglobulins and C3 and C4 complement components were normal. A kidney biopsy (KB) demonstrated a picture of MN. Anti-PLA2R antibody was negative in the serum and PLA2R and THSD7A antigens were not detected in the KB. Three CIDP-associated autoantibodies (anti-contactin 1 (CNTN1), anti-contactin associated protein 1 and anti-neurofascin) were tested by ELISA which revealed the presence of anti-CNTN1 at 1:100 serum dilution. CNTN1 antibody was revealed by immunohistochemistry in the subepithelial immune deposits in the patient’s paraffin biopsy sections but not in control PLA2R-positive KB (figure 1).

Discussion: CNTN1 should be added to the armamentarium of antigens involved in MN and tested in PLA2R negative MN associated with CIDP. Further studies are needed to determine the prevalence of CNTN1-associated MN among patients with CIDP, and in those without CIDP and as yet unidentified antigen.
PO1470

Epitho Epitope Spreading and Immune Complex Rearrangement in Membranous Nephropathy
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Introduction: We present a rare case of ANA and anti-dsDNA negative, anti-GBM positive lupus nephritis (LN) patient with two biopsies demonstrating LN Class III-V with possible immune complex (IC) rearrangement and/or epitope spreading (ES).

Case Description: A 62-year-old white male who presented with a year-long history of purpuric rash and hematuria. His hospital admission laboratory data is detailed in Table 1. The first renal biopsy showed crescents in 2/4 glomeruli with mild (+++) granular and segmentally linear deposits by immunofluorescence (IF). The patient received cyclophosphamide, corticosteroids and one session of thrombopelagic plasma exchange due to rapidly worsening renal function and an initial presumptive diagnosis of anti-GBM disease. The second biopsy demonstrated no crescents but features of combined class III + V LN with IF findings suggestive of a fail-house pattern with a change in the deposits from segmentally linear to pure granular. He began therapy with mycophenolate mofetil and prednisone resulting in a decrease in his UPCR from 2.3 to 0.3 mg/ml (complete remission) over the next four months and significant improvement in renal function.

Discussion: A link has been reported between anti-GBM histopathology and membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-dominant epitopes leading to propagation of autoimmune. Circulating anti-GBM antibodies may continually stimulate the upregulation and alteration of anti-GBM epitopes leading to the development of granular deposits and membranous nephropathy. We believe our case suggests this possible pathogenic mechanism. More research is needed to improve understanding of the sequential change observed on immunofluorescence microscopy.

Laboratory Data

PO1471

Generation of Anti-THSD7A Antibodies Using a Human Antibody Phage Display Library
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Background: Membranous nephropathy (MN) is an antibody-mediated autoimmune renal disease. In the majority of cases, autoantibodies target podocyte membrane proteins such as PLAr21 and THSD7A. We could previously demonstrate that autoantibodies in THSD7A-associated MN cause disease and recognize several extracellular domains of the target antigen. However, the mechanisms underlie this antibody polyclonality relates to disease pathogenicity. The aim of this study was the generation of anti-THSD7A antibodies using a human antibody phage display library for further diagnostic and pathomechanistic studies.

Methods: In the antibody phage display technology, antibody fragments are displayed on the phage particle and the corresponding gene fragment encoding the antibody is packaged in the phage particle. A selection process called panning enables the selection of antibody fragments against virtually any target structure. However, it remains unclear how this antibody polyreactivity relates towards the clinical outcome, which could be investigated by further studies.

Results: Four binders (SAK79-B1, SAK78-C12, SAK78-E6, SAK78-F8) could be obtained. While SAK78-F8 exclusively bound human THSD7A, the other binders reacted with both human and murine THSD7A in Western blot, ELISA and IFT. A domain-specific ELISA revealed binding of SAK78-B1, SAK78-C12 and SAK78-F8 to the regions d9, d11-d2 and d6-d7, respectively. SAK78-B1 did not react with any domain combination, but showed strong binding to murine and human d11-d21. We suspect a conformational epitope that was not conserved in the coated domain fragments. SAK78-C12 and SAK78-E6 were successfully cloned into human IgG subclass backbones IgG1-4.

Conclusions: Antibody phage display represents a powerful method to generate recombinant antibodies. The antibodies selected show different binding characteristics in vitro. In vivo binding characteristics, pathogenicity and potential as a diagnostic tool, e.g. to stain THSD7A in patient biopsies, need to be determined.

Funding: Government Support - Non-U.S.

PO1472

A Comparison of aPLa2Rab Assays on Treatment with Cyclophophamide and Steroids
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Background: Anti-PLa2R antibodies (aPLa2R) are present in ~75% of patients with primary membranous nephropathy (MN). A qualitative immunofluorescence test (IFT) allows accurate detection of aPLa2R, additionally ELISA and ChLIA provide quantitative analysis. Sensitivity of the two latter methods after start of immunosuppressive therapy is not well studied.

Methods: We retrieved stored samples of patients with aPLa2R associated MN, who were treated with cyclophosphamide and steroids (CP), collected at baseline and 8 weeks after start of therapy. Assays were performed by the EUROIMMUN researchlab, Lubeck, Germany. All samples were analysed by IIFT, ELISA and ChLIA. We categorized ELISA results to cut-off values used in literature: 2, 14, and 20 RU/ml resp.

Results: We included baseline samples of 50, and 8 week samples of 51 patients. At baseline, all patients tested IIFT positive; ELISA test was positive in 94% or 98% of samples using cut-off values of 20 RU/ml or 14 RU/ml resp., indicating high sensitivity. Agreement between IIFT and ChLIA was 100%. After 8 weeks on CP, 37/51 patients had immunological remission by IIFT. ELISA test results are given in Table 1.

In the IIFT positive samples collected after 8 weeks, ELISA titers were < 20RU/ml or < 14 RU/ml in 9/14 and 5/14 patients respectively, suggesting lower sensitivity. All IIFT negative samples had ELISA titers < 14 RU/ml. When analysing IIFT negative patients with ELISA titer <2 UL/ml (N=23) vs. 2-14 UL/ml (N=18), persistent immunological and clinical remission was better in the first group (74% vs 58%), however not statistically different. With ChLIA only 4/51 (8%) had different results (2 IIFT+/ChLIA+, 2 IIFT-/ChLIA+); resulting in a sensitivity of 86% and a specificity of 95%, when compared to IIFT.

Conclusions: Using immunological remission as treatment target, as described here after 8 weeks of CP, requires evaluation of the applied assay for this purpose. Of the examined quantitative methods, ChLIA demonstrated the highest agreement with IIFT. ELISA titers below the recommended cut-off for initial diagnosis still show a tendency towards the clinical outcome, which could be investigated by further studies.

Funding: Commercial Support - EUROIMMUN researchlab, Lubeck, Germany.

PO1473

The Classical Pathway Triggers Pathogenic Complement Activation in Membranous Nephropathy
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Background: Membranous nephropathy (MN) is characterized by severe proteinuria, circulating autoantibodies against podocyte antigens such as PLAr21 and THSD7A, and glomerular deposition of IgG and complement components (CCs). However, the pathways triggering the complement cascade (classical, alternative or lectin) and the significance of local glomerular complement action for podocyte damage and proteinuria are poorly understood.

Methods: Complement activation was investigated in 20 biopsies from patients with PLAr21- and THSD7A-associated MN using immunofluorescence and proximity ligations to visualize the assembly of CCs/convertases. Experimental autoimmune MN (EAMN) in C3-/- mice. The efficacy of complement-targeted treatment was evaluated by weekly injection of a C3-silencing siRNA after the onset of proteinuria.

Results: The assembly of the classical/lectin convertase was identified in 19/20 MN biopsies, which was accompanied by detection of IgG and C1q in the majority of cases. The alternative convertase and MBL deposits were detected in fewer cases. Upon immunization, mice developed clinical and histopathological features of MN. Proteinuria ranged from mild to severe nephrotic syndrome and histopathological features included granular glomerular deposition of IgG and CCs including C1q and C3 as well as loss of the podocyte cytoplasmic networks nephrin and nephrin. Strikingly, severe disease with ascites was prevented in C3-/- mice and overall proteinuria was reduced in comparison to WT littermates. Finally, treatment with C3-silencing siRNA after the onset of proteinuria attenuated disease.
Conclusions: The complement system is dominantly activated via the classical pathway in MN patients. Experimental data in the first author’s murine model demonstrate that an antigen that is pathologically relevant in patients suggests complement-targeted treatment as a promising strategy for MN patients with severe disease, but also hint at a role of complement-independent mechanisms in the pathogenesis of MN.

Funding: Government Support - Non-U.S.

POI1474

Positive PLA2R Detection by Mass Spectrometry but Negative PLA2R Staining on Immunofluorescence Microscopy

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Background: Detection of PLA2R along the glomerular basement membranes by immunofluorescence (IF) studies using antibodies directed against PLA2R is considered the gold standard for diagnosis of PLA2R-positive MN on the kidney biopsy. Microdissection of glomeruli followed by mass spectrometry (MS) of PLA2R-positive MN also detects high total spectral counts of PLA2R confirming the IF studies. However, correlation of PLA2R-negative MN cases by IF and MS has not been done.

Methods: We performed laser microdissection and mass spectrometry in 230 cases PLA2R-negative MN in search of novel proteins that may represent new target antigens in PLA2R-negative MN. All 230 cases were negative for PLA2R by IF staining.

Results: We detected high total spectral counts of PLA2R in 8 (3.5%) of the 230 PLA2R-negative MN cases by IF. The mean total spectral count of PLA2R in the 8 cases was 57 (range 24 to 83, SD ± 25.0) (Figure 1). This is comparable to the mean total spectral counts in PLA2R-positive MN (57.7 ± 23.7). The baseline mean total spectral count of PLA2R in 6 time zero transplant biopsies (control cases) was 6. Interestingly, all subtypes of IgG1 were present in the 8 cases that were positive for PLA2R by MS with IgG1 being the dominant (total spectral count 57 ± 16.9) followed by IgG3 (50.0 ± 11.5), IgG4 (46.3 ± 18.1) and IgG2 (39.3 ± 11.4). On kidney biopsy, 3 of the 8 cases showed findings for secondary autoimmune MN such as C1q positivity or full house Ig staining. Electron microscopy showed stage I MN in 2 cases, stage II MN in 5 cases and stage III in 1 case. Clinical details at presentation were as follows: 3 females and 5 males, mean age 53.6 years (± 20.7), mean serum creatinine 1.38 mg/dL (± 0.6), and mean proteinuria 6.8 g/mo/24 hours (± 2).

Conclusions: IF is negative for PLA2R staining in a small (3.5%) number of PLA2R-negative MN. These cases can be detected by IF. Thus, MS is an alternative to IF staining and the new gold standard to detect PLA2R on the kidney biopsy.

POI1475

Can the Use of the Serum Anti-PLA2R Antibody Negate the Need for a Renal Biopsy in Primary Membranous Nephropathy?

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Background: Since the emergence of the anti-PLA2R antibody test, nephrology practice has not changed dramatically, and most nephrologists are still relying on performing a kidney biopsy in diagnosing membranous nephropathy. In this study, we sought to examine how anti-PLA2R antibody tests using ELISA can be utilized in clinical practice.

Methods: We have conducted a retrospective analysis for 187 patients between 2003 and 2020 correlating their renal biopsy findings with their anti-PLA2R antibody test when performed. We have recorded all patient’s demographics, urine protein creatinine ratios, serum albumin, anti-PLA2R antibody test, among other antibodies using ELISA or immunosuppression treatment. Using a statistical analysis model, we have calculated the positive and negative predictive values of the anti-PLA2R at test carried out during that period.

Results: The mean levels of anti-PLA2R antibody titer in primary membranous nephropathy were 217 RU/ml, whereas the mean level was only 3 RU/ml for both secondary membranous nephropathy and other diagnoses. The majority of our cohort who had a positive anti-PLA2R antibody test had a confirmed renal biopsy diagnosis of primary membranous nephropathy with a PPV of 97.3%. Also, we found that the test sensitivity was 75.5%. On the other hand, we found that the NPV was 98.6% and the specificity was 97.8% at a level of ≥20 RU/ml

Conclusions: The anti-PLA2R antibody test is a highly specific test for diagnosing membranous nephropathy. Experience from our center supported by some evidence from the literature suggests that we can rely solely on a positive test without the need to perform a renal biopsy. More prospective trials are required to further validate that notion.

Funding: Private Foundation Support

POI1476

Complement Activation and Suppression Profile Reveals Distinct Subtypes in C3 Glomerulonephritis


Background: The complement pathway is an innate immune defense mechanism, and uncontrolled activation can cause damage to host tissues including the kidney. C3GN is characterized by deposits in the glomerulus made up entirely of complement C3 protein without the presence of immunoglobulins.

Methods: The activity of the alternative complement pathway (ACP) was determined in serum derived from C3GN patients, IgA Nephropathy (IgAN) and Polycystic Kidney Disease (PKD) and healthy controls (HC) by measuring the lysis of rabbit red blood cells (rRBC). Complement factor H (CFH) was added to the serum of C3GN patients to determine if CFH is capable of inhibiting the ACP in C3GN patients.

Results: Analysis of the ACP using the serum of C3GN, IgAN, PKD patients and healthy controls can be calculated by the lysis of rRBC. The percent lysis at specified time points (5, 10 and 15 minutes) was calculated using the maximal lysis for each sample. Serum from C3GN patients result in more significant lysis (one way ANOVA, P = 0.01) at 5 and 10 minutes (22.9% ± 11% and 42.7% ± 12%, respectively) compared to HC (7.1% ± 3% and 21.7% ± 6%, respectively), IgAN (10.9% ± 7% and 27.3% ± 15%, respectively) and PKD (8.6% ± 6% and 24.4% ± 12%, respectively). However, all 3 groups had similar lysis rates in the 15 minutes, suggesting that the ACP is more rapidly activated in C3GN patients, leading to faster depletion of C3. Addition of CFH to the serum of C3GN patients reduced the ACP activity to control levels in 6 out of 14 patients. We did not detect CFH specific antibodies in the serum of patients who did not respond to CFH, indicating additional mechanisms are involved with the rapid activation of the ACP in C3GN.

Conclusions: The ACP is rapidly activated by the serum of C3GN patients compared to other kidney diseases and HC. Although the addition of CFH to the serum reduced the lysis this activation comparison does not extend to all C3GN patients, not all the serum samples responded to CFH. Future work may elucidate additional mechanisms of the continued ACP activation in C3GN patients and have implications for therapy of these patients.

POI1477

Preexisting Autoimmune Dysregulation Unmasks a Role for Silica Dust Exposure in Nephrotropic Autoantibody Production

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Background: Pathogenic autoantibodies (autoAb) promote severe glomerulonephritis in ANCA vasculitis and lupus. Genetic susceptibility and environmental exposures, particularly inhalation of silica (Si) dust, are implicated in dysregulated autoimmunity and are targets for therapeutic intervention. Using a mouse reporter system expressing a regulated nephrotropic autoAb transgene (Tg) targeting basement membrane (BM) and instilling Si by oropharyngeal aspiration (OPA), we demonstrated that central B cell tolerance and anergy to BM are preserved in multiple lupus strains despite induction of lung inflammation and ectopic lymphoid tissue. Nonetheless, Si exposure increased local and systemic anti-DNA Ig levels in wildtype (WT) B6 and lupus mice, suggesting subversion of alternative regulatory checkpoints. Herein we leverage the aberrant M7 anti-BM Tg lineage that demonstrates partial escape from tolerance and evidence of glomerular Ig deposition to study the interaction of Si exposure with preexisting defects in autoreactive cell regulation.

Methods: M7 Tg mice (WT at Ig light chain, or LC, locus) were exposed to Si or vehicle (V) by OPA, organs harvested at 5-6 weeks, and cells cultured with or without CD3/CD28 beads (TLR-L). To restrict Ig specificity, a subset of mice (TgKi) was bred to heterozygosity for the V6/8.9.5 V8R Ig LC knock-in. Tg autoAb were measured by ELISA; mean OD±SD.

Results: Presence of serum Tg autoAb and induction of high levels of autoAb by TLR-L stimulation upregulated splenocytes (OD 2.61±2.49; TLR7/9, v 0.06±0.03; medium, p<0.0001) confirmed Tg phenotype, and bronchoalveolar lavage fluid cell counts confirmed exposure (237±130 ± 18.1±7, x1000, Si vs V, p<0.05). Among Tg WT mice, more autoAb were produced by TLR7/9-stimulated lung cells from Si-exposed mice (OD 0.13±0.15, Si, vs 0.03±0.01, V, p<0.05), indicating that Tg B cells recruited by Si exposure contribute to local autoAb production. Among Si-exposed mice, Tg autoAb levels were higher in Tg WT vs TgKi mice: OD 1.239±0.47 for TLR4-L stimulated splenocytes, Tg, vs 0.51±0.63 TgKi, p<0.05.

Conclusion: An autoAb reporter system reveals that anti-BM autoreactive lymphocytes that escape tolerance can be recruited to the lung after exposure to inhaled silica dust. Anti-BM cell activation by superimposed stimuli, such as TLR-L, can lead to secretion of nephrotropic autoAb.

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Characteristics of Membranous Nephropathy Patients with IgG and IgA Co-Deposits on Capillary Wall

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Background: Membranous nephropathy (MN) is characterized by immune deposits on glomerular capillary wall, predominantly IgG. There have been several reports of MN combined with IgA nephropathy with features of IgA immunofluorescence staining in the glomerular mesangium. However, we found that IgA can also be deposited on the capillary wall with IgG. This study aimed to investigate the prognostic, clinical and renal histopathological characteristics of adult MN patients with IgA and IgG co-deposits on capillary wall.

Methods: A retrospective study was conducted in biopsy-proven MN patients of our renal department during January, 2007 to May, 2020. Clinical data were collected at time of biopsy and the latest follow-up. Pathological parameters included immunofluorescence staining, plaq2r staining, membranous Chang’s stages, sclerosis, crescent, focal segmental sclerosis lesion, chronic tubulointerstitial injury and et al. Indirect immunofluorescence experiment was conducted in 293T cells transfected with plaq2r plasmid.

Results: Out of 531 cases diagnosed with MN, 53 patients have moderate IgA deposit on capillary walls with IgG. 19 cases were determined to be secondary MN, which were 10 cases of autoimmune disease, 4 cases of Hepatitis B, 3 cases of kidney transplantation. 1 case of chemical exposure and 1 case of AL amyloidosis-associated secondary MN. 31 Idiopathic MN patients with both IgA and IgG depositing along capillary wall were followed up for a median interval of 42months (interquartile-range, 17-82) and 3 with IgA only (6.5%) patients progressed to ESKD or death, 2 (6.5%) patients had their eGFR declined by half, 11 (35.5%) patients had no remission and 15 (53.6%) patients were followed up for a median interval of 49months (interquartile-range, 17-82) and 3.

Conclusions: IgA and IgG could be co-depositing on glomerular capillary wall in MN patients, secondary causes should be screened with cation. IgA and IgG type of autoantibodies linked to MN co-existed in serum of idiopathic MN patients, whose prognosis might be poor.

Mystery Cryoglobulinemic Glomerulonephritis Treated with Rituximab

Mohamed Hassanein, Hanny Sawaf, Leal C. Herlitzi, Michael Lioudis. Cleveland Clinic, Cleveland, OH.

Introduction: Cryoglobulinemic Glomerulonephritis (GN) is characterized by the deposition of immunoglobulins (IG), also known as cryoglobulins (CG), in the kidney. We report a case of idiopathic mixed cryoglobulinic GN treated with rituximab and prednisone.

Case Description: A 42-year-old triathlete with a history of pediatric meningitis with hydrocephalus requiring placement of a ventriculoperitoneal shunt presented with lower extremity swelling limiting his ability to exercise. He denied non-steroidal anti-inflammatory drug and illicit drug use, and was not on any prescribed medications. Laboratory workup showed serum creatinine: 1.2 mg/dL (normal 0.7 – 1.2), serum albumin: 2.1 mg/dL (normal 3.9 – 4.9), CG: 140 mg/mL (normal 0 – 50), C3: 39 mg/dL (normal 86 – 166), C4: 7 (normal 13 - 46), and a urine protein to creatinine ratio (UPCR) 5.9 g/g. Kidney biopsy showed diffuse proliferative GN with polyclonal IG deposits consistent with mixed cryoglobulinic GN (figure 1). An infectious workup, including human immunodeficiency virus (HIV), viral hepatitis, blood and urine culture, and a lumbar puncture were unremarkable. Computed tomography of the chest, abdomen, and pelvis revealed splenomegaly. Echocardiogram and bone marrow biopsy were non-diagnostic. He was treated with rituximab and prednisone with normalization of CG, C3, and C4, a reduction in UPCR to 0.5 g/g and return to full exercise capacity five months later.

Discussion: Mixed cryoglobulinic GN is a rare disorder caused by polyclonal deposition of IG in the kidney. Autoimmune disease, hematological malignancies, and infectious etiologies such as endocarditis, HIV, and viral hepatitis should be ruled out prior to immunosuppressive therapy. Our patient elected to proceed with treatment due to his poor quality of life and evidence of end-organ involvement. Although workup for hematological malignancies was unremarkable, it is unclear if his splenomegaly could be reflective of an underlying indolent lymphoma, which could have simultaneously responded to rituximab treatment.
Case Description: 28-year-old African American man with ESKD secondary to biopsy-proven PLA2R-positive membranous nephropathy undergoing a 2/2 mismatch ABO incompatible living-unrelated kidney transplantation. Induction immunosuppression included methylprednisolone and Thymogobulin. Post-op course was complicated by bleeding and he was taken back to the OR on POD 1. Labs showed anemia (Hgb 7.5 g/dl), thrombocytopenia (PLT 25 k/µl), low haptoglobin (< 10 mg/L), high LDH (580 Units/L), low C3 and normal C4. ADAMTS-13 activity and coagulation profile were normal. Graft function was delayed. This raised concern for a TMA. Tacrolimus was not initiated. Allograft biopsy performed on POD 4 confirmed the diagnosis. Eculizumab was administered, resulting in resolution of anuria and hemolysis, and gradual renal recovery. Genetic testing for complement revealed a ‘variant of uncertain significance’ in CFI (Iso357Met). This variant is located in the serum protease domain of Factor 1 which contains the catalytic site. Functional analysis of the variant using recombinant proteins revealed that it had defective complement regulatory activity. This work established that the CFI variant was deleterious and thus defined the etiopathogenesis of TMA in the patient.

Discussion: This is a case of de novo post-transplant aHUS due to a pathogenic complement mutation, likely triggered by transplant surgery. Our strategy of recombinant protein production followed by detailed functional assessment defined the functional repertoire of the variant protein and provided critical guidance relative to the underlying pathophysiology and appropriate therapeutic regimen.

PO1483

Post-Transplant Thrombotic Microangiopathy due to a Pathogenic Mutation in Complement Factor I

Sanaa J. Shaikh, Maryam Saleem, Anuja Java. Washington University in St. Louis Washington University in St. Louis, St. Louis, MO.

Introduction: Thrombotic microangiopathies (TMA) are life-threatening conditions characterized by hemolytic anemia, thrombocytopenia and AKI. Drug-induced TMA (DITMA) is a diagnostic challenge because specific tests to identify a drug etiology are not available.

Case Description: A 40 yr-old female with history of neurofibromatosis type 2 underwent resection of a T10-11 schwannoma. The surgery was complicated by wound dehiscence which was treated with incision and drainage followed by intravenous vancomycin and cefazolin. The next day, she developed fever, altered mental status and a diffuse purpuric rash (Fig 1). Labs showed anemia (Hgb, 6.2 g/dl), thrombocytopenia (PLT, 15k/µl), elevated LDH and anuric AKI requiring dialysis. C3 and C4 were low. Coombs test was negative. She subsequently developed disseminated intravascular coagulation and elevated liver enzymes. Skin biopsy revealed a leukocytoclastic vasculitis with IgG and complement deposition within vessel walls. Given the concern for DITMA versus thrombotic thrombocytopenic purpura, vancomycin was discontinued. Treatment with prednisone and plasmapheresis was initiated which led to improvement of renal function, mental status and hematoctitic parameters within 48 hrs. Renal biopsy confirmed TMA. ADAMTS-13 activity and complement genetic testing came back not available.

Discussion: This is a rare case of vancomycin-induced TMA. We speculate the mechanism is immune-mediated given the presence of low complement levels (although we did not test for vancomycin-dependent antibodies). Patients with immune-mediated DITMA present with sudden onset of severe systemic symptoms after a short exposure to the implicated drug. Greater awareness with improved methodology for diagnosis of DITMA is critical for clinicians evaluating such patients. Recognition of DITMA and documentation of the drug etiology are essential for patient safety.

PO1482

Vancomycin-Induced Thrombotic Microangiopathy: A Rare Association

Gaurav Rajashekar, Anuja Java. Washington University in St. Louis, St. Louis, MO.

Introduction: Thrombotic microangiopathies (TMA) are life-threatening conditions characterized by hemolytic anemia, thrombocytopenia and AKI. Drug-induced TMA (DITMA) is a diagnostic challenge because specific tests to identify a drug etiology are not available.

Case Description: A 40 yr-old female with history of neurofibromatosis type 2 underwent resection of a T10-11 schwannoma. The surgery was complicated by wound dehiscence which was treated with incision and drainage followed by intravenous vancomycin and cefazolin. The next day, she developed fever, altered mental status and a diffuse purpuric rash (Fig 1). Labs showed anemia (Hgb, 6.2 g/dl), thrombocytopenia (PLT, 15k/µl), elevated LDH and anuric AKI requiring dialysis. C3 and C4 were low. Coombs test was negative. She subsequently developed disseminated intravascular coagulation and elevated liver enzymes. Skin biopsy revealed a leukocytoclastic vasculitis with IgG and complement deposition within vessel walls. Given the concern for DITMA versus thrombotic thrombocytopenic purpura, vancomycin was discontinued. Treatment with prednisone and plasmapheresis was initiated which led to improvement of renal function, mental status and hematoctitic parameters within 48 hrs. Renal biopsy confirmed TMA. ADAMTS-13 activity and complement genetic testing came back not available.

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PO1485

Minimal Change Disease as a Novel Manifestation of Cytomegalovirus
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Introduction: Cytomegalovirus (CMV) infection is typically asymptomatic among the immunocompetent or can cause a mononucleosis. Among immunosuppressed patients common presentations are colitis, hepatitis, encephalitis, retinitis and even Guillain-Barre syndrome. This case is a rare dissemination of CMV manifesting as acute glomerulopathy.

Case Description: A 67 year-old female with past medical history of lupus, rheumatoid arthritis, and Sjogrens syndrome on maintenance steroids presented with a prolonged cough, joint swelling, shortness of breath and rash consistent with livedo reticularis. She developed worsening weakness in the arms and legs. High dose IV steroids were initiated for presumed rheumatoid vasculitis. Nephrology was consulted for worsening renal function with urine protein to creatinine ratio of 42 g, later requiring hemodialysis for volume management. Work up for nephritic range proteinuria including hepatitis B/C, HIV, SPEP, UPEP, and complement screen was unrevealing. Renal ultrasound demonstrated an 11.7 cm right kidney and 14 cm left kidney. Renal biopsy demonstrated diffuse podocyte effacement and large atypical mononuclear cells within the glomerulus. No immune deposits seen on electron microscopy. Immunohistochemical staining confirmed glomerular CMV. Six weeks after starting treatment with ganciclovir the glomerulus. No immune deposits seen on electron microscopy. Immunohistochemical staining confirmed glomerular CMV. Six weeks after starting treatment with ganciclovir, CMV viral load was undetectable and renal function recovered to baseline.

Discussion: CMV involvement of the kidney is unusual aside from tubulointerstitial nephritis. Rare cases of collapsing glomerulopathy and focal segmental glomerular sclerosis are found in literature. We report a novel presentation of CMV glomerulopathy with minimal change disease and renal failure. To prevent tissue invasive CMV in a chronically immune suppressed patient one needs to maintain clinical suspicion for infectious pathogens and perform tissue biopsy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO1486

Minimal Change Disease Following the mRNA-1273 Vaccine in a Kidney Transplant Recipient
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Introduction: Kidney transplant recipients (KTR) are susceptible to post-transplant glomerulopathies. Minimal change disease (MCD) is seen rarely. Few cases have been reported post-immunization, recently with the Pfizer-BioNTech vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report a case of de novo MCD after mRNA-1273 vaccine in a deceased donor KTR with sudden onset nephritic syndrome (NS) and acute kidney injury (AKI) a week after the first dose.

Case Description: 45-yo woman with history of ESKD from lupus nephritis, underwent DDKT on 09/2019 from a 20-y Caucasian male, kidney donor profile index 16%, calculated panel reactive antibody 0%. Complicated by delayed graft function. On day 27 post-transplantation serum creatinine (Scr) improved to 0.8 mg/dl. Maintenance immunosuppression tacrolimus and mycophenolic acid. 11 months post-KT contracted COVID-19 pneumonia, managed conservatively. 6 months later developed anasarca 4 days post mRNA-1273 vaccine in a deceased donor KTR, with sudden onset nephritic syndrome (NS) and acute kidney injury (AKI) a week after the first dose.

Discussion: This is a seropositive SARS-CoV-2 KTR from previous COVID-19 pneumonia developed NS. Contrasting mRNA vaccine mRNA vaccines contain mRNA that does not enter the cell nucleus and directs the cell to produce a protein that elicits an immune response. The cell is not infected or damaged. mRNA vaccines transcribed into mRNA, synthesized by the ribosome, translated into protein, and the immune system recognizes and mounts a response. This case may represent a rare association between SAPHO and IgA nephropathy.
Kidney biopsy for IgA case depicting membranoproliferative pattern of glomerular injury in patient with SAPHO syndrome

PO1489
Crescentic Pauci-Immune Glomerulonephritis in a Patient with Sickle Cell Anemia and Cocaine Abuse
Marimar Contreras Nieves, Stanford Medicine, Stanford, CA.

Introduction: Levamisole is an anthelmintic agent and a common contaminant found in cocaine. It has been linked to ANCA-associated vasculitis with cutaneous, and more rarely, renal and pulmonary manifestations. This is the case of a patient with sickle cell anemia and cocaine abuse presenting with acute kidney injury (AKI) and nephrotic-range proteinuria.

Case Description: A 58-year-old male with history of sickle cell anemia, CKD Stage 3, hypertension, and cocaine abuse, was admitted for epidermidis and found to have AKI. He presented with testicular pain, as well as right knee and back pain. Initial workup revealed a creatinine of 2.45 mg/dL, from baseline of 1.8 mg/dL. Urine toxicology was positive for cocaine. His urine studies were consistent with intrinsic renal disease.

He received red blood cell exchange transfusion, but he continued with worsening renal function following the procedure. His 24-hr urine collection revealed 6.2 g proteinuria. Extensive workup included normal C3 and C4, positive rheumatoid factor, negative UPEP, free kappa/lambda light chain ratio 1.8, negative HIV and anti-HCV, hepatitis B immunity, negative c-ANCA, but positive p-ANCA and anti-MPO. Patient chronically smoked cocaine, sometimes cut with levamisole, which is associated with vasculitis.

A kidney biopsy! performed, with pathology showing a pauci-immune glomerulonephritis, necrotizing crescentic glomerulonephritis, transmural arteritis, and sickle cell nephropathy. He was treated with pulse dose steroids and rituximab, followed by maintenance prednisone and additional doses of rituximab after discharge. His renal function improved, but did not return to baseline, which could have been due to his degree of kidney injury and ongoing cocaine use after discharge.

Discussion: This case demonstrates the importance of keeping a broad differential diagnosis in the evaluation of AKI and nephrotic-range proteinuria in sickle cell anemia, particularly in the setting of cocaine use and its known association with levamisole.

Although sickle cell nephropathy could have explained this patient’s presentation, a broader workup was key to arrive to the correct diagnosis, and therefore prompt treatment.

PO1490
A Case of Rapid Progressive Glomerulonephritis Associated with Disseminated Gonococcal Infection
Safa Osman, Nihal M. Ali, Pradeep Varita, Franco H. Cabeza Rivera. The University of Mississippi Medical Center, Jackson, MS.

Introduction: Disseminated gonococcal infection (DGI) results from bacteremic spread of the sexually transmitted pathogen, Neisseria gonorrhoeae. Direct and immunological damage of multiple organs can be seen. We are reporting a case of sterile DGI with RPGN as part of the initial presentation.

Case Description: A 60-years old male with a 5-year history of seronegative spondyloarthropathy, hypertension, heart failure, poor dentition who presented to the hospital with shortness of breathing, diarrhea, joint pain, and palpable purpura ongoing for several weeks. Work-up revealed severe anemia and rapidly progressive acute renal failure (Baseline creatinine unknown, peaked at 7.2 mg/dL on admission), urine showed 9.3 g of proteinuria, hematuria, and pyuria. Serological w/up showed low C3 with normal C4, ASO, ANA, ANCA and anti GBM. Negative HIV, hepatitis B, C, syphilis serologies, monoclonals, and cryoglobulins. Skin biopsy showed leukocytoclastic vasculitis which improved with steroids. Kidney biopsy showed crescentic glomerulonephritis (GN) with 10% IFTA likely due to infectious GN (RPGN). Patient completed 3-day course of ceftriaxone but left before ceftriaxone could be initiated. A week later he presented with persistent hematuria and oliguria. Echocardiogram showed tricuspid endocarditis and leaflet perforation. Blood cultures were negative. Patient started on vancomycin and Rocephin for culture negative endocarditis. Extensive infectious disease workup, metagenomics test showed Neisseria gonorrhoeae as the cause of endocarditis. Kidney function improved. Due to disseminated GC and concern for complement deficiency, he was referred to Adult Immunology clinic.

Discussion: DGI is estimated to occur in up to 3 percent of patients infected with N. gonorrhoeae. The probability that a localized gonococcal infection will spread to joints and other tissues depends upon specific host, microbial, and possibly immune factors.

RPNG is unusual presentation, the immunopathogenesis is uncertain but immunological and hypersensitivity damage is postulated based on the frequent lack of N. gonorrhoeae growth from blood, skin, and synovial fluid cultures during disseminated infection. Congenital or acquired complement deficiencies (C5, C6, C7, or C8) predispose to DGI as a result of decreased complement-mediated killing of N. gonorrhoeae.

PO1491
Proliferative Glomerulonephritis with Monoclonal IgM Deposits in ANCA Vasculitis
Rama Kethineni, Marc Barry, Monica P. Revelo Penafiel, Janane J. Kotkey, Niraj K. Yadav, Josephine Abraham. University of Utah Health, Salt Lake City, UT.

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) is a rare entity of unclear etiology that can be occasionally associated with an underlying hemato logical malignancy. We report a case of PGNMID in a patient with ANCA vasculitis.

Case Description: A 78 yr old female with hypertension presented with a history of recurrent sinusitis over 6 months that was treated with steroids and antibiotics. She had progressive weight loss, fatigue, cough, and dyspnea. Chest X-ray was normal prompting a CT chest, which showed bilateral pulmonary nodules. Her creatinine was 0.96mg/dL. Urine analysis was notable for hematuria. Antineutrophil cytoplasmic antibodies were positive at 1: 640 with myeloperoxidase Abs IgG of 199. Serum protein electrophoresis showed a normal pattern with no monoclonal spike on immunofixation electrophoresis. Her Kappa/Lambda light chain ratio was normal at 1.04, infections were ruled out, and cryoglobulin was not detected. She was started on prednisone 60 mg and had a renal biopsy. Renal biopsy showed focal segmental necrotizing glomerulonephritis, mesangial hypercellularity with deposition of IgM with lambda light chains restriction on immunofluorescence and occasional mesangial and subendothelial granular electron densities on electron microscopy. She was referred to hematology for concern with monoclonal gammopathy of renal significance and had a negative evaluation on serological tests, bone marrow biopsy and PET CT scan. She was treated with Rituximab. Her creatinine had remained stable with resolution of hematuria and respiratory symptoms.

Discussion: PGNMID is an immune complex glomerulonephritis that is occasionally associated with a hemoglobinopathy malignancy. The pathophysiology remains elusive and treatment can be challenging. We present a case of PGNMID with monoclonal IgM with light lambda chain restriction with an unusual association with ANCA vasculitis.
severe interstitial fibrosis and tubular atrophy indicating MPA. Patient was treated with pulse steroid and plasma pheresis initially, later received Rituximab. Patient improved clinically with therapy. Later, serum creatinine plateaued around 3.6 with eGFR 15.6 indicating patient’s CKD had progressed to advanced CKD stage 4/5.

**Discussion:** Though the presence of AAV is not common in MCTD, this case illustrates the importance of considering AAV for worsening pulmonary and renal function in overlap syndrome. Microscopic polyangiitis is one of the most common causes of pulmonary-renal syndrome. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis.

**Case Description:** The patient is a 32-year old woman with diffuse systemic sclerosis complicated by pulmonary fibrosis who had been treated with Mycophenolate mofetil but she discontinued treatment in order to conceive. She reports having an uncomplicated pregnancy without proteinuria or hypertension, but she delivered 7 weeks early. After delivery, she began experiencing weakness of her lower extremities and given steroids for suspecting demyelinating neuropathy and restarted treatment with Mycophenolate mofetil. She had improved but few weeks later (3 months after delivery), she was readmitted with hypertensive encephalopathy in setting of suspected scleroderma renal crisis. She also developed a rash and swelling in her legs after her pregnancy. Her urinalysis was remarkable for proteinuria and numerous RBCs and quantification of the urine protein revealed nephrotic range proteinuria (4.6 g/24 hours) but her serum creatinine (0.6 mg/dl) remained normal. She was found to be positive for antineutrophil antibodies, rheumatoid factor, myeloperoxidase antibodies, MPO-ANCA (> 8.0 IU/mL).

Her complement levels were within normal limits. She underwent a renal biopsy, which revealed an acute necrotizing vasculitis consistent with AAV.

**Discussion:** Clinicians should remain vigilant for concomitant autoimmune disorders in patients with scleroderma. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis, particularly when there is nephrotic range proteinuria or an active urine sediment.

**PO1493**

Nephrotic Range Proteinuria due to ANCA-Associated Vasculitis in a Diffuse Systemic Sclerosis Patient: A Rare Presentation

Pranav Sharma, Steve I. Khalil, Jonathan Lebowitz. Rutgers University New Brunswick, New Brunswick, NJ.

**Introduction:** Scleroderma renal crisis (SRC) is a severe complication of SSc and typically presents with new-onset hypertension and a reduction in renal functioning. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare co-occurrence with SSc. We present a rare case of diffuse systemic sclerosis who presented with features of SRC and AAV with nephrotic range proteinuria without significant renal failure.

**Case Description:** The patient is a 32-year old woman with diffuse systemic sclerosis complicated by pulmonary fibrosis who had been treated with Mycophenolate mofetil but she discontinued treatment in order to conceive. She reports having an uncomplicated pregnancy without proteinuria or hypertension, but she delivered 7 weeks early. After delivery, she began experiencing weakness of her lower extremities and given steroids for suspecting demyelinating neuropathy and restarted treatment with Mycophenolate mofetil. She had improved but few weeks later (3 months after delivery), she was readmitted with hypertensive encephalopathy in setting of suspected scleroderma renal crisis. She also developed a rash and swelling in her legs after her pregnancy. Her urinalysis was remarkable for proteinuria and numerous RBCs and quantification of the urine protein revealed nephrotic range proteinuria (4.6 g/24 hours) but her serum creatinine (0.6 mg/dl) remained normal. She was found to be positive for antineutrophil antibodies, rheumatoid factor, myeloperoxidase antibodies, MPO-ANCA (> 8.0 IU/mL).

Her complement levels were within normal limits. She underwent a renal biopsy, which revealed an acute necrotizing vasculitis consistent with AAV.

**Discussion:** Clinicians should remain vigilant for concomitant autoimmune disorders in patients with scleroderma. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis, particularly when there is nephrotic range proteinuria or an active urine sediment.

**PO1494**

Filgrastim-Induced ANCA-Associated Glomerulonephritis in the Presence of Membranous “Full House Nephropathy"

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**Introduction:** G-CSF is commonly used to stimulate progenitor cell collection for bone marrow transplantation. We present a seemingly healthy altruistic bone marrow donor who developed glomerulonephritis secondary to G-CSF treatment.

**Case Description:** A 34-year old man presented after altruistic bone marrow donation. During G-CSF treatment he developed headache, epistaxis, painless macrohematuria and AKI (creatinine- 2.91 mg/dl). Seven years and one year prior to this event he had similar episodes of macrohematuria, AKI and proteinuria. In between episodes he had persistent microhematuria. All other serologies were unremarkable. A kidney biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis. He soon developed pulmonary hemorrhages. Ivermectin was discontinued. He received prednisone 1mg/kg, 3 biweekly doses of intravenous cyclophosphamide, 10 doses of plasmapheresis, and was given steroids for suspecting demyelinating neuropathy and restarted treatment with Mycophenolate mofetil but she discontinued treatment in order to conceive. She reports having an uncomplicated pregnancy without proteinuria or hypertension, but she delivered 7 weeks early. After delivery, she began experiencing weakness of her lower extremities and given steroids for suspecting demyelinating neuropathy and restarted treatment with Mycophenolate mofetil. She had improved but few weeks later (3 months after delivery), she was readmitted with hypertensive encephalopathy in setting of suspected scleroderma renal crisis. She also developed a rash and swelling in her legs after her pregnancy. Her urinalysis was remarkable for proteinuria and numerous RBCs and quantification of the urine protein revealed nephrotic range proteinuria (4.6 g/24 hours) but her serum creatinine (0.6 mg/dl) remained normal. She was found to be positive for antineutrophil antibodies, rheumatoid factor, myeloperoxidase antibodies, MPO-ANCA (> 8.0 IU/mL). Her complement levels were within normal limits. She underwent a renal biopsy, which revealed an acute necrotizing vasculitis consistent with AAV.

**Discussion:** Clinicians should remain vigilant for concomitant autoimmune disorders in patients with scleroderma. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis, particularly when there is nephrotic range proteinuria or an active urine sediment.

**PO1495**

Ivermectin-Induced ANCA Vasculitis

Shuchi Pandey,1 Hemant Magoo,1 Ashish Verma,1 Sudhir Perincheri,2 Saint Vincent Hospital, Worcester, MA; 2Yale-New Haven Hospital, New Haven, CT.

**Introduction:** Ivermectin is an antiparasitic agent that has demonstrated antiviral potential against HIV-1, Dengue, Zika viruses and most recently, COVID-19. The rampant self-medication and off-label use for COVID prophylaxis in some countries is cause for concern. Here, we present what may be the first reported case of ANCA-associated vasculitis (AAV) from Ivermectin use.

**Case Description:** A 56-year male with no significant past medical history presented with dark urine, epistaxis, conjunctival redness, arthralgias, and malaise. His mother was on dialysis for the past few years for ESRD of unknown etiology. For several months, he had been taking Ivermectin imported from Peru for COVID prophylaxis per family advice. He was on no other medications. His creatinine, normal at baseline, was now 4.5mg/dl. He had hematuria, 3g/d proteinuria, dysmorphic RBCs and RBC casts. Serum C3, C4, ANA, anti-dsDNA, anti-GBM, hepatitisB&C screen, SPEP&UPEP were negative. Atypical and p-ANCA were negative, but c-ANCA was 1:640. Kidney biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis. He soon developed pulmonary hemorrhages. Ivermectin was discontinued. He received prednisone 1mg/kg, 3 biweekly doses of intravenous cyclophosphamide, 10 doses of plasmapheresis, and was initiated on dialysis. Four weeks later, he has no epistaxis or pulmonary hemorrhages and is off oxygen. He does remain dialysis-dependent.

**Discussion:** Drug exposure can trigger ANCA formation against myeloperoxidase (MPO) and, less commonly, proteinase 3 (PR3). Drug-associated AAV can’t be discerned from primary AAV based on clinical and pathological findings. Clues suggesting drug-associated AAV include a temporal relationship of symptom onset with suspected drug, a high ANCA titer, and positive autoantibodies like elastase and myeloperoxidase. Drug-associated AAV has a better prognosis than its primary counterpart, with symptoms often resolving with drug withdrawal. Though this may not suffice in cases with pulmonary and renal involvement, outcomes in drug-associated AAV remain comparable even with shorter induction and often no maintenance regimens. Commonly implicated drugs are hydralazine, levamisole-contaminated cocaine, propylthiouracil, allopurinol.
Although no case of Ivermectin-induced AAV has been reported, we recommend a high
index of suspicion as prompt cessation of the offending drug can significantly improve
prognosis in drug-associated AAV.

PO1496
Myeloperoxidase-ANCA and Takayasu Arteritis Overlap Syndrome
Presenting as Rapidly Progressive Glomerulonephritis

Introduction: The spectrum of vasculitides is classified according to the size of
the vessels involved and the clinical and histopathological findings. The simultaneous
involvement of Takayasu arteritis and myeloperoxidase-ANCA vasculitis is extremely rare
Case Description: A 12-year-old female with no previous medical history. In the last
two years she has developed lower limb claudication and unexplained intermittent
fever. In recent weeks she developed edema and oliguria, she was admitted in another
hospital where she was started on renal replacement therapy. Large vessel involvement
was suspected so a contrast enhanced CT was ordered and was compatible with Takayasu
arteritis. The patient was referred to our hospital for evaluation. During nephrology
assessment she was found to have acute kidney disease with massive proteinuria (16 g/dl),
so work up was directed towards rapidly progressive kidney disease. Percutaneous kidney
biopsy was performed, and it revealed pauci-immune crescentic glomerulonephritis.
ANCAs and glomerular basement membrane antibodies were ordered, with a positive
MPO-ANCA result. She was then started on IV methylprednisolone pulses and 5 cycles of
plasma exchange therapy. After this, rituximab was started on a weekly basis. The
patient has not recovered kidney function and is still dependent on hemodialysis therapy,
pending to finish the final two rituximab doses.

Discussion: This an extremely rare case which highlights the diagnostic and therapeutic
difficulties in patients presenting with overlap clinical and serological features
of different forms of systemic vasculitis.

PO1497
Granulocyte Colony Stimulating Factor-Associated Vasculitis: Adding Fuel to the Fire
Nilem Patel, Ahmed Siddiqui, Pravir V. Baxi. Rush University Medical Center, Chicago, IL.

Introduction: Granulocyte colony-stimulating factor (G-CSF) is commonly used
with chemotherapy to stimulate bone marrow production and prevent neutropenia.
Although usually well tolerated, G-CSF can exacerbate underlying autoimmune
diseases with the development or progression of glomerulonephritis (GN). We present a case
of pauci-immune necrotizing GN that developed in a patient with rheumatoid arthritis (RA)
after receiving G-CSF therapy.

Case Description: A 61 y/o man with ampullary adenocarcinoma and RA without
prior renal involvement presented with AKI. One week prior to admission he had received
5th cycle of FOLFOX and a first dose of G-CSF. His creatinine (Cr) was 4.8 mg/dL
from a baseline of 0.9 mg/dL. His urinalysis was notable for hematuria and urine protein-
creatinine ratio (UPC) of 5.2 g/g. Workup showed: +p-ANCA (1:320), -anti-histone Ab,
+SSA and +ANA (1:1280 speckled pattern). A renal biopsy revealed necrotizing GN with
necrosis or crescents in 75% of the glomeruli. There was no evidence of immune
deposits/c-PAuci-immune GN. He received steroids and rituximab for induction. His
Cr peaked at 6.0 mg/dL but improved down to 1.1 and UPC improved to 0.6 g/g after
3 months.

Discussion: G-CSF is used to prevent neutropenia and reduce infection risk by
activating mature neutrophils and preventing neutrophil apoptosis. G-CSF can also have
inflammatory effects including the release of proinflammatory cytokines and tissue
infiltration by activated neutrophils with the potential of end-organ damage. In patients with
preexisting GN or an autoimmune disease (eg, RA, SLE), G-CSF administration can
exacerbate or even initiate a de-novo GN. Pauci-immune GN is a rare but well established
complication of RA. In our case, the almost immediate temporal relationship between
the development of the GN and the G-CSF administration supports G-CSF as etiologic.
This case demonstrates the importance of considering the possible renal complications
and need for close monitoring while giving G-CSF in patients with autoimmune diseases.

PO1498
Spontaneously Resolved Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits
Salma Shaikhouni, Alexandria M. Peirce, Andrea L. Oliverio, Laura H. Mariani. University of Michigan, Ann Arbor, MI.

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is thought to be a progressive disease, with early studies showing
38% of patients with persistent renal dysfunction and 22% progressing to ESKD within a
30 month follow up period. We present two cases of PGNMID who achieved spontaneous
remission without directed therapy.

Case Description: Case 1: A 53 yo woman with hypertension and diabetes presented
for evaluation of proteinuria with UPCR 3.86 g/g and normal creatinine. She was
asymptomatic, but had an upper respiratory infection 1 month prior. Serologic evaluation
for nephrotic range proteinuria was unrevealing. Renal biopsy showed PGNMID with
IgG A light chain deposits. Serum paraprotein was not detected. Bone marrow biopsy
showed no concern for malignancy. UPCR decreased to 0.63 within 4 months with no
therapy but an ACEi. Case 2: A 53 yo man with primary biliary cholangitis presented
with edema and new hypertension. He was found to have AKI with SCR 1.85 mg/dL,
UPCR of 12.9 g/g, and microscopic hematuria. While serum autoimmune markers were
notable for mildly elevated anti-dsDNA (75 IU/mL), normal C3 and low C4 (8 mg/dL),
renal biopsy revealed PGNMID with IgG A light chain deposits. A low titer IgM k was
detected in the serum. The patient had diffuse lymphadenopathy on imaging, and two
exocytotic biopsies showed reactive follicular hyperplasia. Bone marrow biopsy was
normal. UPCR decreased to 1.23 g/g within 2.5 months of presentation and SCR down to
1.22 without any therapy.

Discussion: These unique cases demonstrate that PGNMID is likely a heterogeneous
disease whose pathogenesis and natural history is poorly understood. We hypothesize
that an infectious antigen or autoantigen may induce clonal proliferation of B-cells and
the formation of transient monoclonal antibodies leading to complement activation
and proliferative glomerulonephritis. When the stimulus is controlled, the associated
immune response is resolved. Our patients did not require any immunomodulatory
therapy, contrary to most recent case series. Recognition of the potential for spontaneous
remission in PGNMID has important implications on treatment paradigms for this
emerging diagnosis.
PO1500

**Pemphigus vulgaris and PLA2R-associated Membranous Nephropathy:**

*Two IgG4-related Diseases in the Same Patient*

Camila L. Costa,1 Matheus R. Correia,2 Luis H. Sette,2 Denise M. Costa,2 Camila B. Oliveira,3 Maria Alina G. Cavalcante,3 Lucila Maria Valente,1 Gisele Vajgel.1 1Hospital dos Servidores do Estado de Pernambuco, Recife, Brazil; 2Hospital Getulio Vargas, Recife, Brazil; 3Universidade Federal de Pernambuco, Recife, Brazil.

**Introduction:** The relationship between bullous skin diseases and glomerulopathies has been increasingly recognised. Other bullous diseases were previously reported in association with membranous nephropathy (MN), but the association between pemphigus vulgaris (PV) and pemphigus vulgaris (PV) has not been reported in the letter between MN.

**Case Description:** A 39-years-old smoker woman presented with trunk blisters and worsened mouth ulcers after stopping the treatment for MN. One year before she had nephrotic syndrome and the kidney biopsy was positive for anti-PLA2R and IgG4 (and negative for THSD7A) in the immunohistochemistry (IHQ). Serum anti-PLA2R was negative. Four months earlier she was started on cyclosporine, but stopped it due to mouth ulcers. She had nephrotic range proteinuria, no edema, when the painful blisters spread out on the trunk, back, limbs, scalp as well as ulcers of the oral cavity and esophagus. The diagnosis of PV was confirmed by skin and esophagus biopsy and IHQ showed the presence of IgG4 subclass antibody in the epithelial tissue. She received pulse and oral steroids along with azathioprine for the PV. The skin lesions were slowly healing and no more new blisters have appeared.

**Discussion:** The humoral auto-immune response in pemphigus produces anti-desmoglein 1 and 3, both IgG4. Desmogleins are responsible for adhesion in stratified squamous epithelia, when damaged produces to the blistering eruptions. There is a genetic predisposition between PV and MN, with HALA-DQA1, HALA-DRB1 and the thrombospondin gene (THSD7A). Environmental factors such as smoking and air pollution could act as a second trigger for the development of auto-immune diseases. PLA2R can be expressed in the bronchiolar tissue and in macrophages of the lung, however there is no evidence of histological damage in the pulmonary tissue. Although we found no description on the expression of PLA2R in the skin, in an attempt to find a common antigen for both diseases, we did search for anti-PLA2R in the skin, but it was negative. In conclusion, this is the first described case of association of pemphigus vulgaris and PLA2R-associated MN, both IgG4-related conditions that involve the production of different autoantibodies directed to skin and kidney antigens.

**PO1501**

A Case of an Elderly Woman with Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits Whose Renal Biopsy Revealed Renal Cell Carcinoma


**Introduction:** Membranous-like glomerulopathy with masked monoclonal IgG deposits (MGIMID) is a recently described form of glomerulopathy with a unique histopathology reported by Larsen et al. The pattern is characterized by subepithelial and/or subendothelial immune deposits that are “masked”, to immunoglobulin staining by routine immunofluorescence but strongly stained for IgG and kappa light chain after protease digestion. Patients with MGIMID are commonly young females and have a vague history of autoimmune diseases such as low titer antinuclear antibodies.

**Case Description:** A 65-year-old woman was referred to our hospital with urinary protein (0.80 g/gCr) and microscopic hematuria. Serum antinuclear antibody, rheumatoid factor, and M-protein were negative and serum C3 and C4 were normal. Plain CT showed no neoplastic lesions in the kidney, and a renal biopsy was performed. Part of kidney biopsy tissue contained clear cell renal carcinoma (RCC). Light microscopy revealed increased mesangial matrix and partial thickening and double contour of the basement membrane. Immunofluorescence examination of the frozen sections was negative for IgG and C3. Electron microscopy revealed electron dense deposits in both the subepithelium and mesangium (Churg classification stage II). After protease digestion, paraffin-embedded sections were stained again, and IgG and kappa light chain were strongly positive in granular pattern along the basement membrane (IgG subclass: IgG1/IgG4). Staining for anti-PLA2R/THSD7A antibody was negative, and staining for anti-serum amyloid P antibody was positive. Based on the above, this patient was diagnosed as MGIMID. Subsequently, she underwent a partial nephrectomy for RCC, and her urinary protein decreased significantly.

**Discussion:** Although most patients with MGIMID are young women (<40 years), this patient was an elderly woman with RCC. IgA nephropathy and membranous nephropathy have been reported as glomerular lesions associated with RCC. In this case, the proteinuria decreased after RCC resection, suggesting that RCC may be related to the development of MGIMID in elderly patients, although the details are unknown. This is the first case of MGIMID in Japan.
polyclonal increase in gamma globulins. It is likely that in some patients with lupus, B cell regulation becomes impaired in a way that allows a clonal, but not necessarily neoplastic, an expansion that results in increased production of paraproteins, leading to MGUS. This case adds to the literature showing that there indeed may be an association between MGUS and lupus.

PO1504

Bartonella Henselae Infective Endocarditis (BHIE): A Rare Cause of Pauci-Immune Necrotizing GN (PINGN)

Muhammad A. Shahzad, Ami Purohit, Stephen M. Korbet. Rush University Medical Center, Chicago, IL.

Introduction: Bartonella is the commonest cause of culture negative endocarditis. While, Infection Related GN (IRGN) can mimic pauci-immune vasculitis, the majority of cases of BHIE have been immune complex (IC) mediated. We present a rare case of BHIE related PINGN. Timely recognition of this atypical presentation led to appropriate medical therapy.

Case Description: A 33 yo M with HIV on HAART and recent tooth extraction was admitted with a severe headache due to a sub arachnoid hemorrhage from a ruptured right anterior cerebral artery aneurysm. TEE showed a vegetation on the aortic valve (AV). Blood cultures were negative. Initial SCR was 3.3 mg/dl and urinalysis had 2+ protein, 3+ blood with 29 RBC/hpf and a UPro/Cr ratio was 1.7 g/l. The C4 was low (10.2 mg/dL) and PR3-ANCA elevated-4.0 (NL <3.5 U/mL). The Bartonella henselae IgG titer was elevated-1.5 (NL <1.320). Renal biopsy revealed pauci-immune necrotizing GN (Figure) with no evidence of IC deposition. BHIE associated PINGN was diagnosed and treatment with doxycycline, ceftriaxone and gentamicin initiated. The AV was replaced and was positive for BH by PCR. After a prolonged course of antibiotics the SCR improved to 2.5 mg/dl.

Discussion: B henselae associated GN is a rare cause of PR3-ANCA positive GN with only 6 cases previously reported. By immunofluorescence, 4 cases were immune complex (IC) mediated. We present a rare case of BHIE related PINGN. Timely recognition of this atypical presentation led to appropriate medical therapy.

PO1505

Atypical Hemolytic Uremic Syndrome and Systemic Lupus Erythematosus-Dermatomyositis Overlap: A Challenging Scenario

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Introduction: Overlap syndromes are rare disorders wherein at least two systemic autoimmune diseases meet diagnostic criteria. We present a case of atypical hemolytic uremic syndrome (aHUS) in a patient with systemic lupus erythematosus (SLE) and anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5) dermatomyositis (DM) overlap.

Case Description: A 45-year-old woman with SLE diagnosed 8mo prior, treated with belimumab and prednisone, developed proximal muscle weakness, violaceous erythema of eyelids, neck, hands and feet with ulcers. Three weeks later, she presented with abdominal pain, shock and respiratory failure. Testing showed WBC 19,200/uL, lipase >600 and ionized calcium 0.47 mmol/L, acute kidney injury (BUN 64 mg/dL, SCR 2.4 mg/dL); anemia (Hb 7.1 g/dL); and thrombocytopenia (PLT 24,000). CT showed pancreatitis and biliary ductal dilatation. Given oliguria and hypocalcemia despite high-dose calcium infusion, she initiated renal replacement therapy. Further workup showed low C3 level 42, C4 level 7, elevated anti-dsDNA Ab 237 IU/ml and UPCR 2.2 g/g; haptoglobin <10, LDH 1,371 U/L. Positive direct Coombs, schistocytes on smear and ADAMTS13 activity 18%. Due to autoimmun vs microangiopathic hemolytic anemia, received pulse therapy with IVIG and IV methylprednisolone and IV cyclophosphamide. She then started eculizumab. Within 7d, LDH decreased to 772, haptoglobin increased to 79 and platelets normalized. Further workup revealed elevated creatinine kinase 1,271 U/L, aldolase 17 U/L, AST 566 U/L with normal ALT and positive anti-MDA5 and transcription intermediary factor 1-gamma (TIF-1γ) Abs, meeting criteria for DM. Patient continued eculizumab and prednisone. Eventually developed invasive aspergillosis and expired.

Discussion: We report a case of SLE-DM overlap with anti-MDA5 and TIF-1γ Abs complicated by aHUS and severe hypocalcemia in the setting of pancreatitis. The cutaneous manifestations are typical of MDA5-associated DM. Our patient did not develop intestinal lung disease, exemplifying range of variation from case to case. The presence of anti-TIF-1γ confers a 6-fold increased malignancy risk; finding of omental nodularity in this case would warrant further investigation. aHUS as a complication of SLE-DM overlap is rare, with mortality risk up to 52%. AKI, infection and low C3 are associated with highest mortality. Prompt diagnosis, high clinical suspicion and early initiation of eculizumab resulted in a rapid response.

PO1506

Anti-LRP2 Nephropathy in a Patient with Chronic Lymphocytic Leukemia

Derek Tran, Chien-Wen Yang, Avantika Israni, Allahbuddin Garea, Al J. Lee, St Mary Medical Center, Langhorne, PA; Penn Medicine, Philadelphia, PA.

Introduction: Anti-LRP2-anti-Brush Border Border nephropathy is a newly identified autoantibodies tubulointerstitial nephritis triggered by circulating antibodies to low-density lipoprotein receptor-related lipoprotein 2 (LRP2). We present a case of anti-LRP2 nephropathy in a patient with chronic lymphocytic leukemia (CLL).

Case Description: A 74-year-old Caucasian male patient known to have CLL presented following a fall with a forearm laceration. At presentation, he had acute renal failure (SCR of 5.04 mg/dl) and severe thrombocytopenia (platelets of 11,000/uL).

Additional evaluation showed positive ANA and p-ANCA. The patient had proteinuria of 1754 mg/g of creatinine. The kidney biopsy showed moderate interstitial fibrosis and tubular atrophy involving 30-40% of the renal cortex. The tubular epithelium showed reactive-appearing nuclei as well as cytoplasmic thinning with loss of the proximal tubular brush border. Immunofluorescence showed IgG(3+) and C3 (3+) for the glomerular capillary and the TBM. There was focal staining of the brush border by IgG with positive LRP2 stain in the TBM. Electron microscopy revealed numerous subepithelial electron-dense deposits. The serum anti-LRP2 antibody titer was 1:100. The patient was started on dexamethasone and rituximab with improvement of the thrombocytopenia. Plasmapheresis was prescribed for 5 sessions, the creatinine continued to worsen (sCr of 7.73 mg/dL), and the anti-LRP2 titer did not improve. The patient is being transitioned to renal replacement therapy.

Discussion: The mechanism that links the ABBA disease with lymphoproliferative disease is still unknown. The current reported cases suggest an association between direct lymphoma renal infiltration, progression of the lymphoproliferative disease and the presence of the ABBA disease. However, in our reported case, the patient’s underlying CLL was stable without evidence of renal infiltration. The poor response to treatment in this case is consistent with the poor outcomes of many anti-LRP2 reported cases. The renal biopsy on this patient also showed membranous glomerulonephritis. We presented a case with anti-LRP2 nephropathy/ABBA disease with concurrent CLL without evidence of LRP2 infiltration which is rare. In our opinion, prompt diagnosis and timely initiation of appropriate therapy the prognosis of ABBA associated paraneoplastic syndrome with underlying CLL warrants future investigation.

PO1507

Black Tar Heroin and AA Amyloidosis

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Introduction: AA amyloidosis due to deposition of serum amyloid A protein occurs as a secondary reaction to chronic inflammatory disease, chronic infections, and familial period fever syndromes. We present a case of AA amyloidosis secondary to chronic black tar heroin use in the Intermountain West.

Case Description: A 61 yr. old Caucasian female with a history of Hepatitis C, IV Heroin use presented with bilateral leg pain, swelling, and abdominal distension. Examination was significant for ulceration in lower extremities with purulent discharges. Notable lab data include Hemoglobin of 8.2 g/dL, potassium of 6 meq/L, calcium of 10.6 mg/dl, BUN of 90 mg/dl, creatinine of 2.9 mg/dl, serum albumin of 2.1 g/dl, and ESR of 129 mm/hour. She had a urine protein to creatinine ratio of 12.3 g/g. Abdominal US revealed enlarged liver and normal renal echogenicity. The quantification of HCV RNA by polymerase chain reaction was negative, and her complement levels were within normal range. Cryoglobulin was also negative with a kappa/lambda light chain ratio of 1.33. Serum protein electrophoresis showed decreased albumin and immunofixation electrophoresis showed a faint band in IgG kappa suggestive of a specific immune response. An early morning bone marrow biopsy showed non-AL amyloid deposition involving glomeruli, and arteries. Mass spectrometry performed at Mayo Clinic Laboratories confirmed renal involvement by Amyloidosis, AA (serum amyloid A)-type.

Discussion: “Black tar heroin” has increasingly been identified as a risk factor for AA Amyloidosis. Impurities in heroin promote vascular sclerosis and lead to the use of injection into muscle and skin. The suppurative infections that follow stimulate

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473
the production of serum amyloid A protein with subsequent deposition in the kidney leading to nephrotic syndrome and end stage kidney disease. Greater awareness of this complication may help prevention in areas with increased black tar heroin use.

**Discussion:** Proteinuria is one of the lesser known side effects of statin therapy. It was reviewed in the clinical development programme for Rosuvastatin, where it was found that the 80 mg dose caused proteinuria in 12% of patients. Furthermore, a comprehensive review of the renal effects of rosuvastatin, found that 1.2% of patients taking 40 mg of rosuvastatin developed 2+ proteinuria, and 0.3% developed 2+ proteinuria and 1+ hematuria. Our case highlights a rare manifestation of Rosuvastatin induced urinary abnormalities, which improve after stopping the drug. This should be kept in mind for patients on Rosuvastatin with negative workup for proteinuria and hematuria, before a renal biopsy is pursued.

**PO1510**

**Rituximab for Membranous Nephropathy in a Patient with Sjögren Syndrome and Mixed-Connective Tissue Disease**

*Joshua D. Pollock, Maurice I. Khayat, Madigan Army Medical Center, Tacoma, WA.*

**Introduction:** Membranous nephropathy (MN), a cause of nephrotic syndrome, is characterized by the deposition of immune complexes in the glomerular basement membrane with resultant subepithelial “spikes” visualized under light microscopy. Although often a primary disease process, several secondary etiologies exist, including Sjögren’s syndrome (SS) and mixed-connective tissue disease (MCTD). Treatment typically targets the underlying condition. Despite rituximab’s demonstrated efficacy in MN, MCTD and SS, case reports for specific treatment of MN secondary to these conditions have primarily described regimens of systemic corticosteroids with or without cyclophosphamide.

**Case Description:** A 54-year-old male was diagnosed with MN on renal biopsy in 2001. Several features suggested secondary etiology (tubulo-interstitial, mild to moderate proteinuria and tubular interstitial chronic injury likely secondary to arteriosclerosis). There was no right hydronephrosis or renal vein thrombosis seen on imaging. Serological testing including ANCA, HBsAg, Hep C ab, HIV, RVP, COVID-19 PCR, Parvovirus B19 PCR, and CMV PCR were all negative. Patient initially received diuretic therapy for LE edema. Kidney biopsy performed during hospital stay showed CG and acute tubular injury. Electrolyte microscopy examination of kidney biopsy specimen was significant for extensive effacement of podocyte foot processes and rare tubuloreticular inclusions in endothelial cell cytoplasm. Scr rapidly worsened to 7.98 and HD treatment was initiated. Our patient was also initiated on daily high dose oral corticosteroid therapy.

**Discussion:** Guselkumab, an IL-23 blocker is FDA approved for the treatment of plaque psoriasis and active psoriatic arthritis. A case of Ustekinumab (IL-12/23 inhibitor) associated FSGS (after 2 years of treatment) has been reported in the literature. Our patient while on chronic Guselkumab treatment developed rapidly worsening AKI and CG, a week following the last dose of Guselkumab. We believe that in absence of any additional known risk factors, Guselkumab was responsible for AKI and CG in our patient. Our patient currently remains dialysis dependent. Clinicians should be aware of this very rare but potential association.

**PO1508**

**Guselkumab-Associated Severe AKI from Collapsing Glomerulopathy**

*Varun Madireddy, Deepa A. Malieckal, Boonyanuth N. Maturotrakul, Philip S. Yune, Vanesa Bijol, Hitesh H. Shah, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

**Introduction:** Collapsing glomerulopathy (CG) has been commonly associated with viral infections, mainly HIV. Several medications have also been associated with CG. We present the first case of Guselkumab-associated rapidly progressive AKI from CG and acute tubular injury.

**Case Description:** 86-year-old African American female with history of HTN, RCC with left nephrectomy, CKD, CHF, and psoriasis (on Guselkumab treatment since 2018) presented to our hospital for worsening bilateral LE edema and AKI. On presentation, Scr was elevated at 3.75 and serum albumin was WNL (3.5). Three weeks prior to presentation, Scr was elevated but stable at 1.77 on outpatient labs. Of significance, pt. received Guselkumab injection one week prior to presentation. During hospital stay, UA was significant for proteinuria and hematuria. Spot urine total protein-to-creatinine ratio (TPCR) was significantly elevated at 13.7. Of note, spot urine TPCR was 1.6, four months prior to presentation. There was no right hydronephrosis or renal vein thrombosis seen on imaging. Serological testing including ANCA, HBsAg, Hep C ab, HIV, RVP, COVID-19 PCR, Parvovirus B19 PCR, and CMV PCR were all negative. Patient initially received diuretic therapy for LE edema. Kidney biopsy performed during hospital stay showed CG and acute tubular injury. Electrolyte microscopy examination of kidney biopsy specimen was significant for extensive effacement of podocyte foot processes and rare tubuloreticular inclusions in endothelial cell cytoplasm. Scr rapidly worsened to 7.98 and HD treatment was initiated. Our patient was also initiated on daily high dose oral corticosteroid therapy.

**Discussion:** Guselkumab, an IL-23 blocker is FDA approved for the treatment of plaque psoriasis and active psoriatic arthritis. A case of Ustekinumab (IL-12/23 inhibitor) associated FSGS (after 2 years of treatment) has been reported in the literature. Our patient while on chronic Guselkumab treatment developed rapidly worsening AKI and CG, a week following the last dose of Guselkumab. We believe that in absence of any additional known risk factors, Guselkumab was responsible for AKI and CG in our patient. Our patient currently remains dialysis dependent. Clinicians should be aware of this very rare but potential association.

**PO1509**

**Proteinuria and Hematuria, an Unfamiliar Side Effect of Statin Therapy**

*Marco B. Thierry, 1, 2 Daniel Varela, 2 Mourad Alsabbagh, 2 Sergio A. Trevino Manillo, 2 Salil Mangi. 1 The University of Texas Rio Grande Valley, Edinburg, TX; 2DHR Health, Edinburg, TX.*

**Introduction:** Statins are among the most commonly prescribed medications worldwide, and have a relatively mild side effect profile. We describe a rare manifestation of statin therapy, with proteinuria and microscopic hematuria.

**Case Description:** A 53-year old Hispanic lady with a history of proteinuria and hematuria for 1 year with negative Urologic workup was referred to nephrology for further evaluation. Patient complained of foamy urine. Her only medication was rosuvastatin 40 mg. Initial UA showed 2+ protein and 5-10 RBC/HFP. Lab work - BUN 16, creatinine 1.0 mg/dL, albumin 4.8 mg/dL. Urine Protein Creatinine Ratio 2.1 g/g creatinine. Serologies were negative and complement levels were normal. Patient was started on ARB and a low sodium diet for proteinuria. Proteinuria persisted and renal biopsy was recommended with suspicion of IgA nephropathy. Biopsy showed mild glomerular and tubular interstitial chronic injury likely secondary to arteriosclerosis. There was no immune complex deposition and no evidence of this basement membrane disease. Genetic workup was negative for Alport’s syndrome. Because of the rare association of Rosuvastatin with urinary abnormalities, we decided to hold patient’s Rosuvastatin. Only three days later the patient reported that foamy urine had resolved. Repeat UPCR showed 99 mg protein/g creatinine. Hematuria also decreased to 0-2 RBC/HFP.
PO1512
C2 Deficiency Associated with Severe Recurrent ANA-Negative Lupus and Necrotizing Glomerulonephritis
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Introduction: Deficiencies in the classical complement pathway have been associated with the development of systemic lupus erythematosus (SLE) and lupus-like disease in 10-20% of affected patients. In fact, SLE patients deficient in classical complement present at an earlier age, with severe manifestations and a worse prognosis. Several mechanisms have been described to explain these immune phenomena including impaired clearance of immune complexes, impaired handling of apoptotic cells, or changes in regulation of cytokines. Here, we present a case of a young female with ANA-negative lupus presenting with dyspnea and acute renal failure responsive to immunosuppressive therapy found to have C2 Complement deficiency.

Case Description: 44-year-old female with sickle cell trait, ANA-negative SLE, ESRD due to biopsy-proven class IV lupus nephritis briefly requiring HD, pulmonary HTN, presented with signs of fluid overload, acute on chronic renal failure in the setting of malignant hypertension. Labs revealed thrombocytopenia of 52 with a creatinine of 2.66 (prior 1.61), hypocomplementemia and undetectable CH50 levels concerning for acute flare of SLE and an underlying functional complement deficiency. Low haptoglobin and peripheral smear with schistocytes raised concerns for microangiopathy. Hospital course was complicated by encephalopathy and possible CNS involvement of lupus. Renal biopsy confirmed chronic sclerosing immune complex glomerulonephritis with minimal activity. The patient responded well to high dose corticosteroids, plasma exchange and mycophenolate mofetil. Final serology confirmed persistent C2 complement deficiency.

Discussion: There is a well-documented link between immune complex disease and complement deficiency. Of these, C2 deficiency is the most common. In our case, a C2 deficiency was found in the setting of ANA-negative SLE with severe clinical manifestations. Our case raises the question of whether testing to exclude underlying complement deficiency is particularly indicated in patients with ANA-negative SLE. It also remains to be seen whether clinical manifestations of microangiopathy are prevalent in these patients, and whether therapeutics targeting complement may be effective in their treatment.

PO1513
De Novo IgA Vasculitis Following Exposure to SARS-CoV-2 Immunization
Terrance Wickman, Muner Mohamed, Agnes B. Fogo, Juan Carlos Q. Velez. Ochsner Medical Center - New Orleans, New Orleans, LA; Vanderbilt University Medical Center, Nashville, TN; The University of Queensland, Saint Lucia, QLD, Australia.

Introduction: Immunizations have been previously described as potential triggering events for development of certain glomerular diseases. However, there is paucity of reports of occurrence of glomerular diseases following exposure to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.

Case Description: A 50-year-old man presented to a nephrology clinic for evaluation of persistent proteinuria. Six weeks prior to evaluation, the patient had reported developing a new rash approximately 2 weeks after receiving the first dose of a SARS-CoV-2 vaccine (Pfizer®). The rash was treated by his primary care provider with topical and oral corticosteroids, leading to partial improvement of the skin lesions. Three weeks after the first vaccine injection, the patient received his scheduled second vaccine injection. Within 2 days, the rash reappeared. This time, the lesions were more severe in nature, with a violaceous papular rash involving his lower legs and with some areas progressing to blisters. He also reported myalgias and arthralgias. A skin biopsy was performed and revealed IgA dominant leukocytoclastic vasculitis. After completion of 2 weeks of oral corticosteroids, a urinalysis revealed proteinuria and a consultation to nephrology was requested. On examination, healing papules were noted on his legs but otherwise exam was normal. Serum creatinine was 0.9 mg/dL. Microscopic examination of the urinary sediment revealed acanthocytes. An urine protein-to-creatinine ratio (UPCR) was 1.1 g/g. Serum complements were normal and all pertinent serology was negative. A kidney biopsy was performed and light and immunofluorescence microscopy findings showed an IgA nephropathy. UPCR decreased to 0.7 g/g and rash completely subsided.

Conclusion: The clinical presentation and pathological findings in this case strongly suggest that SARS-CoV-2 Vaccine (Pfizer®) can trigger a clinical syndrome compatible with Henoch-Schönlein purpura. The recurrence of the rash following re-exposure to the vaccine injection (second dose) argues for a definite causal association by Naranjo criteria.
Discussion: Hydralazine has been known to cause DI-GN since the 1950s, and it can manifest with features of pauci-immune glomerulonephritis and lupus nephritis. Drug-induced vasculitis has a high incidence of renal involvement compared to drug-induced systemic lupus erythematosus, however both entities have multiple auto-antibodies and ANCA positivity. The use of hydralazine has increased over the years due to trials demonstrating mortality benefit in heart failure. There is no consensus on the treatment, but discontinuing the offending agent, early diagnosis, and immunosuppressant therapy may result in favorable prognosis.

Table 1

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PO1516

Chicken or the Egg Causality Dilemma: Primary ANCA Vasculitis Complicated by Infective Endocarditis (IE) vs. IE Leading to ANCA Vasculitis
Benjamin P. Catanese, Ayesha Anwar, Shuchi Anand. Stanford Health Care, Stanford, CA.

Introduction: As the cases of infective endocarditis increase in the United States it is important to recognize the associated complications. Glomerulonephritis is a well-recognized but not fully understood consequence. Immune complex deposition is the most common etiology but ANCA-mediated kidney injury is increasingly described and even less understood.

Case Description: A 65 year old male presented with acute onset dysarthria, left facial droop, left sided weakness, and dizziness. 5 months prior he was diagnosed with PR3+ ANCA vasculitis after presenting with 18 lbs weight loss, purpura, anemia, hematuria and sub nephrotic proteinuria. He was treated with methotrexate and a steroid taper, which finished one week prior to the current presentation. Admission vitals were: 145/74 mmHg, heart rate of 90 bpm, and 100% oxygen saturation on room air. Lab work revealed: hemoglobin of 10.7 K/uL, creatinine of 1.17 mg/dl (baseline 0.9), low C3: 81 mg/dl, positive PR3 (>8.0), positive c-ANCA (1:128), negative MPO and p-ANCA, and U/A: 3+ blood, negative protein, and 11-20 WBC. MIRIs of the brain and heart revealed numerous acute and subacute infarcts and severe mitral regurgitation respectively, concerning for small vessel vasculitis, and he was started on high dose steroids. Discovery of streptococcus mutans bacteraemia was a surprise. Suspicion was raised that the ANCA vasculitis may have been a consequence of underlying sub-acute endocarditis rather than a primary disease hence a kidney biopsy was planned and he was discharged on steroids and IV antibiotics. Kidney biopsy confirmed the diagnosis of ANCA-mediated endocarditis-associated glomerulonephritis with the presence of glomerulosclerosis with fibrocellular/fibrous crescents, segmental fibrinoid necrosis but no obvious immune deposits on light microscopy. Granular deposits in the mesangial and capillary wall stained for C3, IgM, IgA, kappa and lambda. He underwent 6 weeks of ceftriaxone and mitral valve replacement. His renal function is mildly impaired; he is recovering neurologically.

Discussion: Endocarditis-associated GN typically requires treatment of the underlying infection without immunosuppression, but when the injury is primarily ANCA-mediated, this presents a unique challenge in that end-organ damage from vasculitis may not improve without immunosuppression.

PO1517

Crescentic Glomerulonephritis in Sjögren Syndrome
Jake N. Cho,1,2 Danielle Janisson,3 Grant Oakley,1,2 Gary DiPerna. 1 Maine Medical Center, Portland, ME; 2 Tufts University School of Medicine, Boston, MA; 3 Maine Nephrology Associates PA, Portland, ME.

Introduction: Sjögren’s syndrome (SS) is an infiltrative autoimmune disorder involving the parotid, lacrimal and salivary glands causing sicca syndrome. Kidney involvement is variable and most often results in tubulointerstitial nephritis. Glomerular disease is infrequent with MPGN and membranous nephropathy being most prevalent pathologically.

Case Description: Patient is a 21 year old female with SS, hypothyroidism and asthma who was being evaluated for fever and fatigue. Lab evaluation revealed acute kidney injury (AKI) with creatinine rising from 1.0 to 1.8 mg/dl over several weeks. Echocardiogram was concerning for mobile echodensity at the tricuspid valve, but transesophageal echo showed no abnormalities and evaluation for infection was negative. CT showed extensive prominent lymph nodes in the chest, abdomen, and pelvis but lymph node biopsy showed benign reactive hyperplasia without neoplasm. Renal ultrasound showed normal sized kidneys. Urinalysis was positive for trace proteinuria and sediment revealed dysmorphic RBCs. She was started on high dose prednisone and hydroxychloroquine for possible lupus nephritis but due to diagnostic uncertainty and unresolved AKI, kidney biopsy was performed.

Discussion: Kidney biopsy demonstrated plasma rich interstitial nephritis with severe tubulitis consistent with SS. Interestingly, the biopsy showed 3 active cellular crescents out of 21 glomeruli with focal crescentic GN. Tubulointerstitial nephritis is the most common renal pathology in primary SS leading to renal tubular acidosis, impaired concentrating ability and proximal tubule defects. GN in SS is rare but has been associated with membranoproliferative GN, membranous nephropathy and cryoglobulinemic GN. Crescentic GN was unexpected and the treatment plan was adapted to taper the prednisone, start on Mycophenolate Mofetil and trial on Rituximab.

Light microscopy for renal biopsy of Sjögren’s case depicting interstitial nephritis and crescentic glomeruli

PO1518

Crescentic Glomerulonephritis and Membranous Nephropathy: A Case Report of a Rare Overlap
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Introduction: Membranous nephropathy (MN) is a disease that affects the basement membrane of the glomeruli of the kidney resulting in proteinuria. The concurrent incidence of vasculitic glomerulonephritis and MN in the same patient is unusual. Herein, we report a case with this unusual combination.

Case Description: Our patient is a 53-year-old Hispanic male with a past medical history of tobacco use, type 2 diabetes mellitus, and hypertension who presented with hematuria and was found to have nephrotic range proteinuria and renal impairment. Blood workup revealed positive ANCA serology, which led to a renal biopsy that showed crescentic vasculitis in addition to membranous nephropathy. The patient was started on intermittent hemodialysis (HD) and treated initially with intravenous (IV) pulse steroids; subsequently, oral prednisolone and IV cyclophosphamide was initiated. The patient remained HD dependent at the time of discharge with the resolution of hematuria. A follow-up with an outpatient nephrology clinic was arranged.

Discussion: Membranous nephropathy complicated by crescentic glomerulonephritis has a more aggressive clinical course and decline in renal function compared to MN alone which can lead to initiating renal replacement therapy. However, immunosuppressive drugs can result in significant improvement of renal function if started early enough.
PO1519

Unmasking a Case of Membranous-Like Glomerulopathy with Masked IgG-κ Deposits
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Introduction: Membranous-like glomerulopathy with masked IgG-κ deposits (MGMID) is a recently described, exceedingly uncommon entity of glomerular immune-complex deposition requiring antigen retrieval on formalin-fixed paraffin-embedded tissue. We report a rare case of MGMID in a young female with newly diagnosed APLA.

Case Description: An 18 year old female with no medical history presented with left leg swelling. Vital signs were normal and an enlarged, discolored left lower extremity was appreciated on exam. Initial laboratory results were remarkable for Cr 0.78 mg/dL, albumin 2.3 g/dL, platelets 128,000/µL, PTT 87.1 s, INR 1.02, and hematuria and foamy urine. Spot urine protein:creatinine ratio was 10 and albumin was 1.6 mg/dL. The creatinine had slowly risen over several months from 0.9 mg/dL to a plateau of 1.8. Serologic work-up was unrevealing; PLA2r, complements, hepatitis serologies, ANA, ANCA, A1C, SPEP, immunofixation, and free light chains were all normal. Renal biopsy demonstrated amorphous deposits throughout the glomeruli which stained positive for serum amyloid A (SAA) (figure 1). We found no systemic causes to explain secondary amyloidosis. This case demonstrates a possible association of secondary amyloidosis with HIV.

Discussion: Only a few case reports have described an association of secondary amyloidosis with HIV. SAA renal amyloidosis has been described in a patient who acquired HIV via intravenous drug use. It was unclear if it was related to the HIV disease or to chronic inflammation from skin infections due to needle use. Renal amyloidosis has also been occasionally described in South African patients with HIV and in non-human primates with HIV-like disease. Elevated levels of amyloid A protein have been found in AIDS patients, suggesting a possible pathogenetic linkage. More studies are needed in this area to determine if there is a causal relationship between the two disorders and what is the best approach for management.

PO1520

A Case of Secondary Renal Amyloidosis Associated with HIV

Introduction: Secondary amyloidosis is known to be associated with multiple chronic infections and inflammatory conditions including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and tuberculosis. HIV has not yet been established as a known association. We present a case of secondary amyloidosis associated with well-controlled HIV with no history of other potential etiologies.

Case Description: A 71-year-old man with hypertension and well-controlled HIV for 40 years (viral load undetectable and last CD4 917) was referred to the renal clinic for acute kidney injury and heavy proteinuria. He had complained of leg swelling and foamy urine. Spot urine protein:creatinine ratio was 10 and albumin was 1.6 mg/dL. The creatinine had slowly risen over several months from 0.9 mg/dL to a plateau of 1.8.

Serologic work-up was unrevealing; PLA2r, complements, hepatitis serologies, ANA, ANCA, A1C, SPEP, immunofixation, and free light chains were all normal. Renal biopsy demonstrated amorphous deposits throughout the glomeruli which stained positive for serum amyloid A (SAA) (figure 1). We found no systemic causes to explain secondary amyloidosis. This case demonstrates a possible association of secondary amyloidosis with HIV.

Discussion: Only a few case reports have described an association of secondary amyloidosis with HIV. SAA renal amyloidosis has been described in a patient who acquired HIV via intravenous drug use. It was unclear if it was related to the HIV disease or to chronic inflammation from skin infections due to needle use. Renal amyloidosis has also been occasionally described in South African patients with HIV and in non-human primates with HIV-like disease. Elevated levels of amyloid A protein have been found in AIDS patients, suggesting a possible pathogenetic linkage. More studies are needed in this area to determine if there is a causal relationship between the two disorders and what is the best approach for management.
**PO1521**

Renal Cell Carcinoma Presenting as Henoch-Schönlein Purpura with AKI and Leukocytoclastic Vasculitis in Adults

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**Introduction:** Henoch-Schönlein purpura (HSP) is a small vessel vasculitis characterized by IgA tissue deposition. HSP presenting in adults is often the result of an underlying malignancy.

**Case Description:** A 60-year-old man with history of HTN, CVA, DMII, recent COVID-19 infection, presented for 2 week history of petechiae on bilateral upper and lower extremities. Skin biopsy findings were compatible with leukocytoclastic vasculitis (LCV). Patient on admission was also found to have AKI with creatinine 2.1 mg/dl, microscopic hematuria, and sub-nephrotic range proteinuria with urine protein/creatinine ratio of 2.66 g/g. Kidney biopsy findings were consistent with IgA dominant glomerulonephritis. Given multi-system involvement, patient was diagnosed with Henoch-Schönlein Purpura. Given unusual presentation with extreme of age, there was concern for malignancy. CT scan chest abdomen pelvis was performed which revealed a solid and septated 8.3 cm exophytic mass on the superior pole of left kidney. A partial left nephrectomy was performed with pathology report consistent with clear cell renal carcinoma. Patient’s hematuria, proteinuria and skin rash resolved with surgical intervention. Creatinine remained stable in the 1.6-1.8 mg/dl range on discharge.

**Discussion:** Henoch-Schönlein purpura (HSP) is generally seen in the first decade of life. There have been a few cases of HSP presenting in adults due to underlying solid organ malignancies including renal cell carcinoma (RCC). Our case illustrates the importance of evaluating adults presenting with clinical findings of HSP for underlying malignancy. Treatment of underlying malignancy will improve vasculitis symptoms including renal parameters.

Exophytic and sepatated mass within superior pole of left kidney (Figure 1).

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**PO1522**

A Case of Necrotizing Crescentic Glomerulonephritis due to ANCA Vasculitis and Fibrillary Glomerulonephritis

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**Introduction:** Fibrillary Glomerulonephritis is a rare disorder thought to be idiopathic in nature. Cases of fibrillary GN have been associated with malignancy, monoclonal gammopathy, autoimmune disease, or infection. We present a unique case of fibrillary GN with pauc-immune crescentic GN due to Myeloperoxidase antibody (MPO) vasculitis.

**Case Description:** A 77 year old lady with history of well controlled diabetes, hypertension, congenital deafness, presented with weakness, fatigue & weight loss for four weeks. She was noted to have severe anemia with Hemoglobin of 6.6 g/dl, and presumed acute kidney injury. Her labs on admission were remarkable for creatinine 2.5mg/dl (unclear baseline creatinine), eGFR 25ml/min, potassium 5.3, Bicarbonate 16, Sodium 128. Urinalysis showed large blood and + protein. The serological workup was positive for P ANCA 1:640, C ANCA 1:640, MPO ab and negative for PR-3 ANA, SREP. Free light chain ratio, HIV, Hepatitis panel. Endoscopy and Colonoscopy was negative for any obvious bleeding. Patient underwent renal biopsy which showed 7 out of 15 glomeruli with early fibrocellular crescents with fibrinoid necrosis, along with healing phase of necrotizing arteritis. Immunofluorescence didn’t show any preferential staining for immunoglobulins, kappa or lambda. Electron microscopy showed mesangial mild non-branched randomly arrayed thick fibrils with no immune complex type deposits. EM findings were confirmed by positive DNAJ9B9 stain. Patient received treatment with pulse dose steroids, two doses of rituximab 1 gm 14 days apart and continued on prednisone for slow taper with good renal response. Due to the findings of Fibrillary GN addition workup for lymphoproliferative disorder was done Whole body CT scan was negative but flow cytometry testing still pending.

**Discussion:** We present a unique case of fibrillary GN and pauci-immune crescentic GN with positive MPO antibodies. The significance of fibrillary deposits in this setting is unclear and usually not seen with pauci-immune crescentic GN. Fibrillary GN is a very rare diagnosis mostly thought to be idiopathic in nature. This unique presentation of fibrillary GN with ANCA vasculitis questions the current pathogenesis fibrillary GN and overall renal prognosis in association with glomerular pathologies like ANCA vasculitis.

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**PO1523**

An Unexpected Clue in the Urinary Space: The Overlap Between IgA Predominant Staphylococcus aureus-Associated Glomerulonephritis and IgA Nephropathy: A Case Report

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**Introduction:** There is significant histological overlap between IgA nephropathy (IgANP) and IgA predominant Staphylococcus-aureus associated glomerulonephritis (IgASAAGN). [1] [1] Satoskar et al., “Staphylococcus Infection-Associated Glomerulonephritis Mimicking IgA Nephropathy,” November 2006.

**Case Description:** Kidney biopsy was performed in a 60 yo male for an unexpected decline in kidney function. IgASAAGN was diagnosed on histology and foreign particles that were consistent with staphylococci were noted in the urinary space on electron microscopy. The patient was found to have methicillin-sensitive staphylococcus aureus (MSSA) pneumonia. Two months later, after a second decline in kidney function, IgANP was diagnosed on repeat kidney biopsy.

**Discussion:** This patient was diagnosed with two distinct conditions on pathology samples that show very similar histological findings. The presence of SA in the urinary space is a previously unreported finding. SA infection is known as the initiating factor for the development of IgASAAGN. Recent studies have also suggested SA cell envelope antigens as a new candidate for the induction of IgANP and antigens have been colocalized with IgA deposits in the glomeruli of affected patients. [2] SA infection and IgA deposition seem to play an essential role in the pathogenesis of both conditions, and the consideration that they may be two extremes of a disease spectrum could be considered. If the role of SA in the development of IgA nephropathy is confirmed, it may be of interest to explore the role of anti-staphylococcal antibodies in the treatment regimen of IgANP. [2] Koyama et al., “Staphylococcus Aureus Cell Envelope Antigen Is A New Candidate for the Induction of IgA Nephropathy.”
PO1525
Diagnostic Dilemma: Glomerular IgG Deposit with Negative Anti-GBM Antibody
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Introduction: Linear deposition of IgG along glomerular basement membrane (GBM) is hallmark of anti GBM glomerulonephritis. Subclass IgG3 deposition is seen predominantly in these cases. Rare atypical anti-GBM cases have been described in literature as rare, indolent, no pulmonary involvement and undetectable antibodies. We describe a case of atypical anti GBM, four days after mRNA COVID vaccine.

Case Description: A 77-year-old male with history of hypertension presented with hypertensive emergency and acute kidney injury 4 days after first COVID vaccine (mRNA). Workup revealed sCr 2.6 mg/dl (1.5 mg/dl 1 month back), 3+ blood and 3+ protein by UA, normal C3, C4, ANA 1: 160, spot urine protein: creatinine- 2.2, serum albumin- 4g/dl, anti ds-DNA, ANCA and anti-GBM antibody was negative so was Hepatitis panel and HIV. Serum electrophoresis was negative for monoclonal protein. He did not have any pulmonary symptoms and CXR was negative for acute pathology. Renal biopsy was performed. LM: mild to moderate nodular mesangial expansion, mildly increased mesangial cellularity and focal segmental nodular mesangial sclerosis. IF showed positive linear global capillary loop staining with IgG (2+), with kappa (1+) and lambda (2+) co-staining. Trace mesangial IgM and granular C3 (trace1+) are also noted in the peripheral capillary loops. EM showed diffuse foot process effacement. Few subepithelial, intramembranous and mesangial electron dense deposits were seen. Additional IgG subclasses IF showed positive linear glomerular staining for IgG1 (3+), IgG2 (1+), IgG4 (1+), negative for IgG3.

Discussion: Although no definitive active glomerular crescents or necrotizing lesions were seen, positive linear IgG staining in the glomerular capillary loops was concerning for atypical anti-GBM disease in setting of negative antibody and negative IgG3A. A study looking at 20 atypical anti-GBM patients found that 1 year patient and renal survival was 93% and 85% respectively. A few patients in this study had biopsy findings of DFPE and sub-epithelial deposits like ours. There have been few reports of COVID vaccine unmasking glomerulonephritis. However, it needs further investigation.

PO1526
Rapidly Progressive Glomerulonephritis due to Crescentic IgA Nephropathy in the Setting of HIV

Introduction: In patients with HIV-related kidney diseases, the most widely recognized histological abnormality is focal segmental glomerulosclerosis (FSGS). Less commonly found is IgA nephropathy in HIV patients, which tends to have a chronic stable course. We report a case of crescentic IgA nephropathy and FSGS in a patient with rapidly progressive glomerulonephritis and newly diagnosed HIV.

Case Description: A 34-year-old transgender woman with a history of alcohol use disorder presented with a petechial rash and lower extremity edema for 1 week, and was found to have a new diagnosis of HIV with an elevated creatinine. CD4 count was 143 and viral load was 103,774, and she was started on renally-dosed dolutegravir, abacavir and emtricitabine. Creatinine on admission was 1.27 mg/dl (baseline 0.7), and increased over the next several days to 5.3. Urine microscopy revealed dysmorphic RBCs and granular casts, with spot urine protein:creatinine 2.3. Renal biopsy demonstrated crescentic IgA nephropathy (Oslo classification M1 E1 S1 T1 C2) with concomitant FSGS (NOS subtype). Cellular crescents were seen in 4/7 glomeruli (figure 1), mesangial and endocapillary hypercellularity in all non-sclerotic glomeruli, and FSGS in 2/7 glomeruli. Immunofluorescence showed strong granular segmental mesangial staining for IgA (3+) and C3 (3+), and was otherwise negative. She was started on pulse-dose steroids (methylprednisolone 500mg x 3 days followed by 1 mg/kg x 2 weeks), as well as plasmapheresis every other day for 5 sessions. Her renal function had not improved by the time of discharge.

Discussion: To our knowledge this is the first reported case of IgA-induced RPGN in the setting of newly diagnosed HIV. A few prior case reports describe stabile IgA nephropathy in individuals with HIV, suggesting that there may be some unifying pathogenesis. This case highlights the need for investigation of this potential mechanism, which may help determine the optimal therapy for IgA nephropathy and IgA-induced RPGN in the setting of HIV.
POI1527
Features and Outcomes of Patients with C1q Nephropathy in the NEPTUNE and CureGN Cohorts: Comparisons to Minimal Change Disease and Focal Segmental Glomerulosclerosis
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Background: Predominant immunostaining for C1q distinguishes a subset of patients with primary glomerular disease. C1q nephropathy (C1qN) has been proposed but not universally accepted as a distinct glomerular disease. This study describes clinical characteristics and short-term outcomes of patients meeting the provisional CureGN definition of C1qN, including comparisons to patients with minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) without C1qN.

Methods: MCD and FSGS patients with C1qN were identified from the Cure Glomerulonephropathy Network (CureGN) and NEPTUNE cohorts. Comparisons were made to MCD and FSGS patients without C1qN, based on age, disease, and time since kidney biopsy, using 5-to-1 matching. We performed cross-sectional analyses of clinical and treatment data at enrollment and a longitudinal analysis of disease course.

Results: A total of 42 patients met the provisional CureGN definition for C1qN (16 adults >18yo, 11 teens 12-18yo, and 15 children <12yo), including 15 with MCD and 27 with FSGS. Those with C1qN were more commonly female (60 vs 49%, p=0.2) and black (34 vs 27%, p=0.4). At enrollment, those with and without C1qN had comparable kidney function (eGFR 90 vs 88 mL/min/1.73m², p=0.8). Individuals with C1qN were equally likely to have been treated with steroids or other immunosuppressive therapy (76 vs 81%, p=0.4) and to have ever achieved complete remission of proteinuria (defined as uPCR <0.3) (54 vs 65%, p=0.2). Median time to last follow-up was 3.1 yrs (IQR 1.9, 4.4) from enrollment and 4.8 yrs (IQR 3.3, 6.5) from biopsy date. While proportions with kidney failure were higher for FSGS compared to MCD (14 vs 1%, p=0.01), they were similar between patients with and without C1qN (7 vs 10%, p=0.6). There was a trend towards steeper GFR slope in C1qN patients (4.8 vs -0.2 mL/min/yr, p=0.06).

Conclusions: FSGS and MCD patients with and without C1qN have comparable demographics and short-term outcomes in CureGN and NEPTUNE. Outcomes do not appear to be biased by differences in immunosuppressive therapies. Further interrogation of genetic and molecular profiles between patients with and without C1q immunostaining on biopsy may be more informative.

Funding: Private Foundation Support

POI1528
Morphologic Descriptors Most Predictive of Clinical Outcomes in Minimal Change Disease and FSGS
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Background: Previous studies applying the NEPTUNE Digital Pathology Scoring System (NDPSS) uncovered the value of kidney tissue features for clinically relevant patient subcategorization. This study aims to identify ultrastructural descriptors most predictive of clinical outcomes in NEPTUNE patients.

Methods: 39 glomerular, 9 tubulointerstitial, 2 vascular, and 20 ultrastructural descriptors were quantified using the NDPSS on 39 MCD, 61 MCD-like, and 124 FSGS NEPTUNE digital kidney biopsies. Outcomes included time from biopsy to disease progression (kidney failure or a 40% eGFR decline with eGFR <90) and first complete remission (CR) of proteinuria (UPCR <0.3). Relative importance of descriptors for prediction of outcomes was obtained from random forest models, without adjusting for clinical features.

Results: The mean age, eGFR and UPCR at biopsy for the total 224 participants was 28.8, 85.2, and 5.4, respectively. Model performance was excellent (predictive discrimination 0.902 for disease progression and 0.853 for CR). Most predictive descriptors included conventional (e.g., global sclerosis or segmental sclerosis, and interstitial fibrosis/tubular atrophy) and unconventional features [Fig]. Top 10 predictors included inflammation, podocyte abnormalities, and acute tubular injury for both outcomes; deflation, interstitial foam cells, and collapse for disease progression; and endothelial cell abnormalities, hyalinosis, and periglomerular fibrosis for CR.

Conclusions: Most predictive descriptors of proteinuric glomerulopathies reflected structural changes in various renal compartments. Reporting these descriptors should be standardized to guide the subcategorization of proteinuric glomerular diseases and improve targeted clinical care.

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Underline represents presenting author.

480
Proteinuria End Points and Associations with Renal Survival in FSGS:
Analysis of the UK National RaDaR Idiopathic Nephrotic Syndrome Cohort

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Background: In patients with FSGS, severity of proteinuria (PU) at onset and during follow up is associated with renal failure. In this study, we tested for associations between defined PU endpoints and renal survival in patients with FSGS from the UK National Registry of Rare Kidney Diseases Idiopathic Nephrotic Syndrome (RaDaR-INS) Cohort.

Methods: A total of 225 biopsy-proven or monogenic FSGS pts met study eligibility criteria, including a nephrotic PU value (≥3.5 g/g), a follow-up PU within 6-12 mo. and no ESKD (eGFR <15 mL/min/1.73m²) or death prior to first PU follow-up. Baseline pertains to first nephrotic PU value (T0 for survival analyses). Applied PU responder/non-responder definitions are described (Table 1). Time to ESKD/ death was analysed using accelerated failure time modelling of the Weibull distribution.

Results: Within 6-12 mo. from baseline, 63% of patients achieved complete or partial remission (CR/PR), while 37% were non-responders (NR). Applying the FSGS partial remission of PU endpoint (FPRE) and including CR patients, 49% met this definition (CR/PR), while 37% were non-responders (NR). A higher probability for survival was observed among patients achieving remission definitions (Figure 1), extending median time to ESKD/death by ≈8 years for CR/PR vs NR, and ≈17 years for CR/FPRE-R vs NR (Table 1) independent of initial PU level. Further analyses are ongoing.

Conclusions: Achieving partial or complete remission of PU is associated with clinically meaningful increases in time FSGS patients are alive and free from ESKD.

Funding: Commercial Support - Travere Therapeutics

PO1531

Clinicopathological Characteristics of Adult Patients in the United States with Focal Segmental Glomerulosclerosis (FSGS)

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Background: Focal segmental glomerulosclerosis (FSGS) is a common histopathologic lesion of glomerular injury in patients with nephrotic syndrome. These analyses characterize clinical and histological features of FSGS in adults at time of kidney biopsy.

Methods: A retrospective study was performed using data from the Arkana Biopsy Database (January 1, 2016 to May 31, 2020) in patients that met study criteria, which included: a18 yrs, aFSGS positive kidney biopsy, and no prior kidney transplant, and available data on race/ethnicity. Outcomes included clinical and histologic characteristics. eGFR was calculated using CKD-EPI-creatinine equation without race modifier.

Results: Of 64,105 adult kidney biopsies performed during the study period, 2,065 (3.2%) FSGS positive cases were identified and 1,482 pts (71.8%) evaluated met study criteria. Demographic characteristics included: 56.2% male, 55.1% White, 32.1% African American (AA), 7.7% Hispanic and 3.4% Asian. Overall mean (SD) age at biopsy was 49.0 (17.2) with older ages in Whites (52.8 (17.3) yrs) and younger ages in Hispanics (39.4 (15.8) yrs). Mean urine protein to creatinine ratio was similar by race/ethnicity (range 5.1-6.0 g/g). Asians were more frequently biopsied at eGFR Stage 4 (32.7%) compared to other race/ethnicity groups: AAs (29.0%), Whites (23.1%), and Hispanics (18.7%). The highest rates of ≥50% global glomerular sclerosis (GCS) were observed in AAs (31.1%) and lowest in Whites (14.6%). Whites (51.9%) and AAs (39.7%) exhibited the highest rates of severe foot process effacement (≥80%), while interstitial fibrosis and tubular atrophy ≥50% was more common in AAs (34.6%) compared to Hispanics (27.2%), Asians (17.7%) or Whites (14.6%). Of all FSGS types, “not otherwise specified” was most common across all race/ethnicity groups (range 64.2-75.4%). Among other FSGS types, tip lesion was most frequent in Whites (21.5%) and collapsing was most frequent in AA patients (12.4%).

Conclusions: Non-White patients are more frequently diagnosed with FSGS at later CKD stages with advanced GS. Strategies to improve earlier awareness and detection of FSGS are needed to allow effective intervention before severe kidney damage has occurred.

Funding: Commercial Support - Travere Therapeutics

PO1532

Long-Term Outcomes of Patients with Focal and Segmental Glomerulosclerosis Treated with Tacrolimus

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Background: Tacrolimus (TAC) is used to treat Focal and Segmental Glomerulosclerosis (FSGS). Prolonged treatment is often required and there is little data on long-term outcomes.

Methods: This is a retrospective study of 29 patients who received TAC as first line immunosuppression for nephrotic syndrome (NS) secondary to FSGS from December 2007- January 2020 at our institution.

Results: Mean follow up was 59.6 months (12-144). The mean age at diagnosis was 42 years (range 18-85). 52% were Male. 59% were White, 10% Black, 21% Asian, 3% Chinese, 7% Other. Baseline mean eGFR was 64 mL/min (18-90). 23/29 (79%) obtained complete (CR) or partial remission (PR) of NS, at a mean time of 5.09 months (range 1-31 months). 6/29 (21%) did not enter remission with TAC. 2/6 subsequently achieved
remission with CyP and prednisolone/rituximab. 7/23 (30%) patients who achieved remission with TAC had at least one relapse, 4/7 after stopping TAC, 1/7 during TAC wean and 2/7 with therapeutic TAC levels. 4/7 were treated by restarting or increasing TAC, 1/7 also had steroids added, 1/7 received rituximab (achieving remission) and 1/7 was not further treated with immunosuppression. 4/4 restarted with TAC monotheraphy reached remission. 16/23 (70%) patients did not relapse and 7 of these remain off TAC and in remission (mean follow up of 92.6 months). At 1 year, the mean eGFR was 67.4 ml/minute (21-90). 1/29 patient developed end-stage kidney disease (ESKD) at 2 months. This patient had not responded to TAC, 16 patients have 5-year-follow up. The mean eGFR was 66.5 ml/minute (11-90). 1 further patient developed ESKD (this patient had not responded to TAC nor subsequent immunosuppression). 4 patients have 10-year follow-up. The mean eGFR was 80.8 ml/minute (67-90). 3 further patients developed ESKD. 1/3 had achieved PR, 1/3 had achieved CR but had multiple relapses despite re-treatment and 1/3 had CR but defaulted from follow up, presenting with ESKD 6 years later.

Conclusions: The long-term data from this study suggests tacrolimus can be effective in both achieving and maintaining remission of NS in FSGS. CR is associated with good long-term outcomes in most patients although relapse can occur and long term careful follow up is required. Non-responders have a worse outcome, although some patients do respond to alternative immunosuppression.

PO1533

Collapsing FSGS in a Patient with Acute Myeloid Leukemia and Prior COVID-19 Infection

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Introduction: Collapsing focal segmental glomerulosclerosis (c-FSGS) has been independently associated with COVID-19 infection, acute myeloid leukemia (AML), and apolipoprotein L1 (APOL1) risk variants. We describe a patient with homozygous APOL1 G1 risk allele and AML who developed renal failure due to c-FSGS and acute tubular injury.

Case Description: A 25-year-old male with a history of mild asthma and COVID-19 infection 1 month prior presented with a 3-week history of severe fatigue, weight loss, persistent dyspnea, and fevers. He was found to have leukopenia, thrombocytopenia, an acute kidney injury, and nephrotic range proteinuria. The patient was diagnosed with AML by bone marrow biopsy (BMMBs). At presentation, his serum creatine was 2.8 mg/dL, which rapidly increased to 6.9 mg/dL over 2 weeks. Urine protein:creatinine ratio (UPCR) was 3.4g/L on admission. Renal biopsy demonstrated c-FSGS (Figure) and diffuse acute tubular injury. He was treated with standard remission induction therapy for AML with 7+3 therapy (7-day continuous infusion of cytarabine, daunorubicin on days 1-3, and an inhibitor, associated with MCD exist. TNF-α inhibitors are increasingly utilized for the treatment of several autoimmune conditions. They have been associated, in rare cases, with renal complications. We report a patient who developed minimal change disease (MCD) and interstitial nephritis while being treated with infliximab (IFX) for ulcerative colitis (UC).

Case Description: A 48-year-old male with a history of primary sclerosing cholangitis, liver transplant 8 years prior, psoriasis, and UC well-controlled on monthly IFX presented with a one-week history of lower extremity swelling, dyspnea, and weight gain. He was found to have rapidly progressive renal failure and nephrotic syndrome. Laboratory data showed a serum creatinine of 11mg/dL up from 1mg/dL 3-weeks prior and urine protein:creatinine ratio (UPCR) of 11g/L. Renal biopsy demonstrated acute interstitial nephritis (AIN) on light microscopy. Electron microscopy revealed global podocyte activation and foot process effacement, consistent with MCD (Figure). He continued to become progressively oliguric despite escalating doses of diuretics and received two days of hemodialysis due to volume overload. After a total of 7 days of high dose steroids, his urine output increased and hemodialysis was stopped. IFX was discontinued due to the association of TNF-α inhibitors with MCD and AIN. After a month of prednison, his creatine improved to 1.6 mg/dL and UPC improved to 0.33g/L.

Discussion: This is the first report of IFX associated MCD. Although IFX has been associated with IgA nephropathy, crescentic glomerulonephritis, renal artery occlusion, membranous glomerulopathy, and AIN in patients with spondylarthritus spectrum diseases, no reports exist in the literature regarding MCD. However, several case reports of Etanercept, another TNF-α inhibitor, associated with MCD exist. TNF-α inhibitors are implicated in immunoregulatory effects in the kidney, which are not well understood.

PO1534

Role of LDL-Apheresis in Management of Glucocorticoid-ResistantMinimal Change Disease

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Introduction: Minimal Change Disease (MCD) is described as diffuse podocyte foot process effacement on kidney biopsy, resulting in nephrotic proteinuria, >3 grams/day. Glucocorticoids (GC) are the mainstay of therapy and most patients achieve complete remission in a few months. 7-12% patients, however, have GC-resistance and thus limited treatment options. Often, they are suspected of having focal segmental glomerulosclerosis (FSGS) due to biopsy sampling error. We present a challenging case of GC-resistant MCD, managed with immunosuppression, and ultimately lipid (LDL) apheresis.

Case Description: An otherwise healthy 20-year-old male presented for sudden onset lower extremity swelling and 10-pound weight gain. Work up including ANA, C3, C4, p-ANCA, c-ANCA, serum and urine immunofixation and renal ultrasound were unremarkable. Notably, LDL was 390 mg/dL and proteinuria of 9 grams/day and serum creatinine (Scr) of 0.96 mg/dL. Kidney biopsy revealed diffuse podocyte effacement, consistent with MCD. He was treated with oral prednisone 1 mg/kg/day and diuretics for several weeks with minimal symptomatic improvement and had worsening kidney function, Scr 1.5 mg/dL and proteinuria of 36 grams/day. Unfortunately, he also contracted COVID-19 disease prior to second kidney biopsy. Repeat kidney biopsy revealed acute tubular necrosis along with widespread podocyte effacement, without sclerotic lesions, ~10% interstitial fibrosis and tubular atrophy. He was empirically treated with tacrolimus for FSGS. However, proteinuria continued to worsen and peaked at 83 grams/day. Ultimately diagnosed as GC-resistant MCD, he was weaned off steroids, he was referred for LDL-apheresis therapy. He is maintained on tacrolimus and LDL apheresis with symptomatic improvement, still has significant proteinuria of 67 grams/day and advanced chronic kidney disease (CKD).

Discussion: The exact pathophysiology of nephrotic syndromes is unclear, mechanisms of T-cell dysfunction causing production of glomerular permeability factor and nephrotic hyperlipidemia have been described. In cases of GC-resistant diseases, immunosuppression has only been partially successful. LDL-apheresis has a role in the management of such nephrotic syndromes, thought to reduce circulating lipid induced disruption of podocyte integrity, and help prevent decline of kidney function and decrease proteinuria as seen in this patient.
PO1536
Anti-Phospholipase A2 Receptor Antibody Levels in Asian Patients with Primary Membranous Nephropathy: A Territory-Wide Study
Desmond Y. Yap, Irene Yam, Michelle Lam, Hemlata Binsuauthsing, Tak Mao D. Chan. University of Hong Kong, Hong Kong, Hong Kong.

Background: Different cut-off values of anti-phospholipase A2 receptor (anti-PLA2R) antibody for differentiating between primary membranous nephropathy (PMN) and secondary membranous nephropathy have been reported. The optimal anti-PLA2R levels to reflect disease activity states in Asian patients with PMN remain undefined.

Methods: We conducted a territory-wide study in Hong Kong to investigate the serum anti-PLA2R levels in Chinese patients with PMN during 2017-2020. Anti-PLA2R levels were measured by commercial ELISA kits (Euroimmun, Germany) in serum samples collected from biopsy-confirmed PMN patients during active disease or remission, and their predictive values for active PMN were evaluated.

Results: Forty and six serum samples from 320 PMN patients were analysed. 319 samples were obtained during active disease and 87 during disease remission. Anti-PLA2R titres during active diseases were significantly higher than that during remission (95.1±235.0 RU/mL vs. 19.3±9.3 RU/mL respectively, p<0.001). Using 20 RU/mL as cut-off, the sensitivity (SN) and specificity (SP) for predicting active disease were 39% and 98% respectively [AUC 0.68, p<0.001; positive predictive value (PPV) and negative predictive value (NPV) were 98% and 30% respectively]. Using 10 RU/mL as cut-off, the SN and SP for diagnosing active PMN were 46% and 95% respectively [AUC<0.71, p<0.001; PPV and NPV were 97% and 32% respectively]. Anti-PLA2R titres correlated with urine protein-to-creatinine ratio and 24-hr urine protein levels (r=0.32 and 0.37 respectively, p<0.001).

Conclusions: Anti-PLA2R showed good SP and PPV prediction for active PMN in Chinese patients, and correlated with severity of proteinuria. A lower threshold (10 RU/mL) may show improved SN for predicting active PMN in Asian patients.

PO1537
Qualitative and Quantitative Dosage of the Anti M-Type Phospholipase A2 Receptor Autoantibody: One-Year Experience in Quebec’s Reference Center
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Background: Dosage of the M-type phospholipase A2 receptor antibodies (anti-PLA2R) in serum is an essential tool for diagnosis and management of primary membranous nephropathy (MN). Since October 2018, Hôpital Maisonneuve-Rosemont (HMR) has been designated as Quebec’s reference center for serum anti-PLA2R antibody testing by the Institut National d’Excellence en Santé et Services Sociaux (INESSS), the regulatory body on drugs and tests usage in Quebec.

Methods: All patients who had serum anti-PLA2R antibody testing performed at HMR from October 1st, 2018 to October 1st, 2019 were included in the study. Serum anti-PLA2R antibodies were screened by a qualitative test, followed by a quantitative test if the results were undetermined or positive. We calculated sensitivity, specificity, predictive value, and likelihood ratio for both tests, using kidney biopsy findings as the gold standard.

Results: In the province of Quebec, a total of 1690 tests were performed among 1025 patients during the study year. A small proportion of these patients (8%) were followed at HMR from October 1st

PO1538
Clinical Relevance of NELL1 Antibodies in Patients with Membranous Nephropathy
Linda Reinhard, Benedict Krümpelmann, Thorsten Wiech, Rolf A. Stahl, Elion Hoxha. 1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2EUROIMMUN Medizinische Labordiagnostika AG, Lubeck, Germany; 3Medizinisches Versorgungszentrum Hamburg-Sinstorf der MVZ gGmbH der PHV, Hamburg, Germany.

Background: PLA2R and THSD7A antibodies (ab) are considered to be specific for the diagnosis of membranous nephropathy (MN). There is a controversial discussion whether the detection of circulating PLA2R- or THSD7A-ab is sufficient to diagnose MN, without the need of a kidney biopsy. We conducted a territory-wide study in Hong Kong to investigate the serum anti-PLA2R levels in Chinese patients with PMN during 2017-2020. Anti-PLA2R levels were measured by commercial ELISA kits (Euroimmun, Germany) in serum samples collected from biopsy-confirmed PMN patients during active disease or remission, and their predictive values for active PMN were evaluated.

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Conclusions: Anti-PLA2R showed good SP and PPV prediction for active PMN in Chinese patients, and correlated with severity of proteinuria. A lower threshold (10 RU/mL) may show improved SN for predicting active PMN in Asian patients.

Funding: Government Support - Non-U.S.

PO1539
Non-Pathogenic THSD7A Antibodies in a Patient with No Membra- nous Nephropathy
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1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2EUROIMMUN Medizinische Labordiagnostika AG, Lubeck, Germany; 3Medizinisches Versorgungszentrum Hamburg-Sinstorf der MVZ gGmbH der PHV, Hamburg, Germany.

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Funding: Government Support - Non-U.S.

PO1540
Urinary NPHS2-mRNA in Relation to Glomerular and Tubular Damage Markers in Patients with Membranous Nephropathy
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Background: Measurement of podocyte-specific mRNA in patients’ urine samples has been proposed as a novel tool to monitor podocyte loss in glomerular disease, and may have prognostic value. In our hospital, we routinely measure timed urinary excretion of high- and low-molecular weight proteins as prognostic markers in patients with membranous nephropathy (MN). Here, we investigated the relationship between NPHS2-mRNA and high- and low-molecular weight proteins in patients with MN.

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483
Continuous variables are expressed as Median (interquartile range). Correlations are expressed in Spearman’s R2 (p-value). UAlib = Urinary albumin, UPod = Urinary NPHS2 mRNA.

Figure 1. UPodCR correlations with protein markers of glomerular injury.

Table 1. Characteristics of patients with membranous nephropathy (N=35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
<th>Median (IQR)</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>102</td>
<td>(10.2; 24.6)</td>
<td>4.1</td>
<td>75.17</td>
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<td>UPCR (mg/mg creat)</td>
<td>102</td>
<td>(10.2; 22.3)</td>
<td>1.9</td>
<td>53.2</td>
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<tr>
<td>UPodCR (mg/mg creat)</td>
<td>102</td>
<td>(10.2; 25.3)</td>
<td>4.1</td>
<td>52.6</td>
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<tr>
<td>UAlib (mg/dL)</td>
<td>102</td>
<td>(14.2; 74.2; 220)</td>
<td>0.19</td>
<td>13.03</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>102</td>
<td>(37.7; 67.5; 145)</td>
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POI541
Urine Biomarkers Predict Treatment Response in the MENTOR Study
Pratha Patipramponpit,1 Sarah M. Moran,1 Gary Bader,1 Chiangjiang Xu,1 Paul C. Boutros,1 Fernando C. Fervenza,1 Sean Barbour,1 Daniel C. Cattran,1 Heather N. Reich1,5 for the MENTOR investigators1 University Health Network, Toronto, ON, Canada;2 Bhumirajangarvinda Kidney Institute, Bangkok, Thailand;3 The University of British Columbia, Vancouver, BC, Canada;4 Queen’s University, Kingston, ON, Canada;5 University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada;6 University of California Los Angeles, Los Angeles, CA;7 Mayo Clinic Minnesota, Rochester, MN;8 Mayo Clinic Florida, Weston, FL.

Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. The outcome of patients with MN is highly variable and clinical parameters do not reliably identify which patients will respond to immunosuppressive therapy (IS). In the MENTOR trial >40% of subjects did not achieve complete or partial remission (CR/PR) of proteinuria by 12 months despite IS with rituximab or cyclosporine, exposing them to unnecessary IS and portending potentially poor prognosis. We evaluated whether a panel of urinary molecular markers of kidney inflammation and fibrosis improves the ability to identify treatment responders in the MENTOR trial beyond clinical data alone.

Methods: We measured the abundance of 55 urinary cytokines, metalloproteases and their inhibitors at the randomization in 104 subjects using a Luminex-based multiplex assay. The primary outcome of interest was achievement of CR/PR at 12 months.

Results: Patients achieving CR/PR had significantly higher CrCl (94.25 ± 31.42 vs 75.17 ± 28.52 mL/min/1.73m2, p<0.002) and lower anti-PLA2R titre (168.5 IQR 20.5,341 vs 549 IQR 115.5,1345 U/mL, p = 0.0002) at baseline. Stepwise selection identified 3 clinical variables (CrCl, PL2AR, treatment) and 8 urinary proteins (IL9, IL10, GM-CSF, VEGF-A, TGFB, MMP2, MMP3, MMP10) associated with CR/PR. A model including the clinical and molecular variables improved discrimination of patients who are predicted to achieve CR/PR compared to a model containing clinical variables alone (ANOVA test p-value = 1.30x10^-3, AUC 0.81 ± 0.096 vs. 0.70 ± 0.109).

Conclusions: In summary, measurement of a panel urinary molecular markers improves the ability to predict remission at 12 months in patients with MN. Improved prediction of patients resistant to standard therapy using non-invasive markers has potential to offer more individualized treatment, to spare unnecessary treatment toxicity and to identify patients who may benefit from trials of novel therapeutic agents.

POI542
Use of Urinary Proteins as Predictors of Response to Immunosuppressive Treatment in Membranous Nephropathy
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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. Progression is defined by remission in proteinuria. Response to immunosuppression agents such as calcineurin inhibitors and rituximab vary. While the presence of anti-PLA2R antibodies may help to guide prognosis and treatment strategies, further identifying biomarkers that could refine treatment decision would be useful. Using data from the MENTOR trial (NEJM 2019), we evaluated whether 24-hour total urinary protein, urinary albumin, immunoglobulin M (ulgM), immunoglobulin G (ulgG), and urinary alpha 1 microglobulin (u1m) at baseline could be used to predict response to immunosuppressive therapy at 12 months in patients with MN.

Methods: Logistic regression models were used to study the relationship between baseline urinary proteins with patients’ treatment outcomes by treatment drug (rituximab or cyclosporine). The treatment outcome was defined as patients achieving either complete (CR; <0.3g/24 hours) or partial remission (PR; 0.3–<3.5g/24 hours) of proteinuria at 12 months.

Results: In both cyclosporine and rituximab arm, all urinary proteins exhibited a decline from baseline to 12 months post treatment. However, none of the baseline urinary proteins were found to be significantly associated with treatment response at 12 months (p>0.05 for all). Results were similar when restricted to patients with positive anti-PLA2R at baseline.

Conclusions: Baseline measures of the urinary albumin, ulgM, ulgG, and u1m are not predictors of patients going into CR or PR at 12 months after treatment with rituximab or cyclosporine.

Table 1: Odds ratio of urinary protein predicting CR or PR at 12 months in patients treated with Rituximab or Cyclosporine (Fully Adjusted model)

*Adjusted for adjust for age, sex, eGFR, and creatinine clearance

POI543
APOL1 High-Risk Genotype Is Associated with Worse Renal Outcomes in Black Patients with Membranous Nephropathy

Background: Black patients have a higher propensity for progression to end-stage kidney disease (ESKD) and this disparity persists in glomerular diseases studied thus far. Genetic variants in the Apolipoprotein L1 (APOL1) gene contribute to kidney disease burden in those with African ancestry. To date, there are no data on the role of APOL1 risk alleles in outcomes among black patients with membranous nephropathy (MN).

Methods: Sanger sequencing for APOL1 risk allele genotyping was completed on patients of African-American ancestry (self or clinician reported) with diagnosis of MN enrolled in the Glomerular Disease Collaborative Network (GDCN) or Cure Glomerulonephropathy Network (CureGN) with DNA samples available were included.

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patient with MN and metastatic breast cancer who developed nephrotic syndrome after receiving her second mRNA-1273 COVID-19 vaccine with positive PLA2R Ab by ELISA suggesting MN flare.

Case Description: A 62 year old female with history of Stage IIIIB T3N3M1 ER/PR positive HER-2 negative metastatic left breast invasive ductal carcinoma, hypertension, and hyperlipidemia presented with bilateral leg edema and proteinuria 2 weeks after COVID-19 vaccination. She had previous proteinuria of 7029 mg/24hr in August 2018 with PLA2R Ab 128 RU/mL in October 2018. She underwent modified radical mastectomy in September 2018 followed by adjuvant chemotherapy in November 2018, after which PLA2R Ab decreased to <2 RU/mL. In February 2019 and urine protein/Cr ratio (UPCR) decreased to 1094 mg/g Cr in April 2019. She was diagnosed with metastatic breast cancer and started anastrozole transiently. She received mRNA-1273 COVID-19 vaccines in late January and February 2021. In March 2021, she presented with bilateral leg edema, dyspnea, and bilateral pleural effusion. Urinalysis had >1000 protein, 24hr urine protein 11.2 g, Cr 1.6 mg/dL, and PLA2R Ab 787 RU/mL. Renal biopsy showed immune complex-mediated glomerulopathy with positive PLA2R, consistent with primary MN stage II-III. Glomerular basement membrane deposits were strongly positive for IgG. Electron microscopy showed numerous subepithelial and occasional intramembranous electron-dense immune-type deposits. She was treated with lisinopril and furosemide followed by rituximab in May 2021. Prior to rituximab PLA2R Ab was 342 RU/mL and UPCR was 8671 mg/g Cr.

Discussion: There is insufficient data on the risk of flare after COVID-19 vaccine in glomerular diseases. There have been a few case reports of primary MN and minimal change disease after COVID-19 vaccine as well as MN after influenza vaccine. Our case of primary MN flare after COVID-19 vaccine adds support to a potential association between SARS-CoV-2 antigens and loss of tolerance to the PLA2R antigen. Close follow-up of patients with primary MN and other glomerular diseases after COVID-19 vaccination is warranted.

PO1546
Primary Membranous Nephropathy Concurrent with ANCA-Positive Crescentic Glomerulopathy in a Hispanic Man
Leonardo Pozo Garcia,1,2 Daniel Varela,1,2 Steffi Sathyaraj,1,2 Mourad Alsbagh,2 Sergio A. Trevino Manlio,2 John Manlio,3 The University of Texas Rio Grande Valley School of Medicine, Edinburg, TX; 2DHR Health, Edinburg, TX; 3South Texas Kidney Specialists, McAllen, TX

Introduction: Primary membranous nephropathy (MN) is a common cause of glomerular disease in adults usually presenting with nephrotic syndrome. Crescents are an unusual finding in MN; its presence suggests a concomitant disease process, such as pauci-immune anti-neutrophil cytoplasmic antibody-related (ANCA) glomerulonephritis (GN).

Case Description: A 36-year-old Hispanic man presented with a 1-week history of malaise and lethargy. Examination revealed an obese Hispanic man with rules on lung auscultation and lower-extremity edema. Laboratory results showed a serum creatinine (sCr) 8.8 mg/dL, BUN of 34 mg/dL. Urinalysis revealed 4+ protein, 25-50 red blood cells per hpf. Spot urine protein creatinine ratio (UPCR) was 19 g/g, p-ANCA titer 1:640. Urine toxicology screen was positive for cocaine. Other serologies and imaging were unremarkable. Renal biopsy showed MN with PLA2R positive staining as well as necrotizing and crescentic glomerulonephritis. Interstitial fibrosis and tubular atrophy were seen only in 10% of the sample. Management was initiated with a pulse of steroids followed by a taper, and renally dosed oral cyclophosphamide. The patient was initiated on hemodialysis due to uremic symptoms and volume overload. Three months after initiation of therapy, urine output significantly improved. Laboratory data showed: a 24 hours urine creatinine clearance of 31 ml/min, sCr 2.9 mg/dL, and UPCR 5.3 g/g. Patient was euolemic. Hemodialysis was discontinued.

Discussion: MN and ANCA GN are distinct manifestations of renal injury with different clinical, laboratory, and pathology findings. Our case highlights an individual with both entities. We hypothesize that the patient’s renal findings of p-ANCA and crescentic GN were likely associated with levamisole adulterated cocaine in the background of primary MN. The patient discontinued cocaine use after our discussions. We decided to treat the patient’s MN with immunosuppressive therapy. Fortunately, the patient has responded favorably to our management with significant improvement in renal function.

PO1547
Clinical-Pathological Features of Podocyte Infolding Glomerulopathy
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Background: Podocyte infolding glomerulopathy (PIG) is characterized by presence of microstructural aggregates originated from cytoplasmic infoldings of podocytes in the glomerular basement membrane (GBM). Few PIG cases have been reported and the significance of this morphology is still unclear. This study aims to elucidate the incidence, clinical-pathological features and prognosis of PIG.

Methods: Renal biopsies with PIG features from January 2018 to December 2020 in Kingmed Diagnostic Laboratory were reviewed. Patients were divided into three groups according to their clinical and pathological findings.
Results: Among 87452 biopsies, 116 (1.37%) cases were found to have features of PIG and 61 patients among them had complete clinical data and follow-up information. Most PIG cases were accompanied with other glomerular diseases, among which were 39 cases (63.9%) with lupus nephritis (Group PIG-LN), 14 cases (23%) with other glomerulonephritis such as membranous nephropathy, focal segmental glomerulosclerosis (FSGS), and minimal change (Group PIG-MCN). Only 8 cases (13.1%) were presented with pure PIG with absence of immunoglobulins and complement deposits. In the PIG-LN group, most patients revealed presence of immunoglobulin deposits, with IgG in 84.6% of the patients, C3 in 74.4% and C4 in 69.2%. Similarly, electron dense deposits were seen in PIG-N (65.9%) and PIG-GN (57.1%) in accordance with immunofluorescence, but there is no significant difference in levels of proteinuria, hematuria and creatinine among the three groups. Most patients in PIG-LN group showed increased ANA tier (100) and decreased C3 level (84.6%). The patients in the pure PIG group showed more sensitivity to glucocorticoid therapy and got a significantly higher complete remission rate (75%) than those in group PIG-LN (53.8%) and group PIG-GN (14.3%).

Conclusions: PIG is a special type of podocyte injury, which is either a separate disease entity or concomitant with other GN, among which LN is the most frequent one. Patients with pure PIG tend to be more sensitive to glucocorticoid therapy compared with those coincide with other GN.

Different degree of PIG.

PO1549
Kidney Outcomes in Biopsy-Proven Thrombotic Microangiopathy with Eculizumab Therapy
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Background: There are limited long-term data on kidney outcomes in eculizumab-treated patients with biopsy-proven thrombotic microangiopathy (TMA). We report our experience of using eculizumab in patients with primary (genetic/antibody mediated) TMA, secondary TMA syndromes associated with antiphospholipid syndrome (APS) or systemic lupus erythematosus (SLE), as well as TMA of undetermined etiology.

Methods: We reviewed adult patients with kidney biopsy-proven TMA treated with eculizumab between 2014-2019. Transplant recipients, pregnant patients and those with scleroderma, shiga-toxin related hemolytic uremic syndrome or thrombotic thrombocytopenic purpura were excluded. Kidney response to eculizumab at 26 weeks for patients not on kidney replacement therapy (KRT) and for those requiring KRT at the time of or within 1 week of an episode of initiation of eculizumab, was defined as an increase in eGFR of 15 mL/min/1.73m² and liberation from KRT respectively. Death within 26 weeks was considered lack of response.

Results: We collected data on 16 patients (primary TMA [n=3]; secondary TMA including SLE [n=3] and APS [n=4]; TMA of undetermined etiology [n=6]). The median time from biopsy diagnosis to treatment initiation was 3.0 days (IQR: 1.0, 10.0) and the median duration of therapy was 303 days (IQR: 160, 604). 13 patients (81%) required KRT at the time of initiation of eculizumab. 4 patients died during follow up, 2 of whom died within 6 (37.5%) weeks of initiating eculizumab. Kidney response, defined as a patient required KRT when therapy was started. 2 of 3 patients who did not need KRT initially eventually progressed to end-stage kidney disease after 1 and 5.5 years from treatment initiation. 3/6 patients (50%) and 3/8 patients (37.5%) with mild and moderate interstitial fibrosis and tubular atrophy (IFTA) (IFTA) on biopsy respectively responded to therapy, whilst those with severe IFTA (n=2) showed no response.

Conclusions: Although eculizumab use has been expanding rapidly for primary and secondary TMA syndromes, our data depicts a suboptimal kidney response, which appears independent of the need for KRT at treatment initiation. Severity of IFTA may be a predictor of kidney response to eculizumab. We suggest that more data is needed on long-term kidney outcomes with eculizumab across TMA syndromes before universally adopting this expensive therapeutic strategy.

PO1550
Recurrence of Atypical Hemolytic Uremic Syndrome After Kidney Transplantation: A Prospective Cohort Study
Caroline Duineveld, Romy N. Bouwmeester, Khoa L. Wijnmsa, Nicolas Van De Kar, Jack F. Wétzels. CUREiHUS study group Radboudumc, Nijmegen, Netherlands.

Background: Since 2016, aHUS patients in the Netherlands are treated with a restrictive treatment protocol. Withdrawal of eculizumab is considered after a treatment period of three months. Furthermore, kidney transplantations in aHUS patients are performed without eculizumab prophylaxis, with initiation of eculizumab in case of post-transplant recurrence. This restrictive treatment protocol is monitored in the CUREiHUS study. Here, we present the CUREiHUS study results for kidney transplant patients.

Methods: All kidney transplant patients who received eculizumab therapy for a suspected aHUS recurrence, and who were included in the CUREiHUS study (after informed consent), were evaluated.

Results: In the period from January 2016 until October 2020 we included 15 (F 12, M 3; median age 42y, range 24-66) patients with suspected aHUS recurrence after kidney transplantation. Patients were classified as high (N=8) or moderate (N=7) recurrence risk. The time-interval to recurrence showed a bimodal distribution. Seven patients presented early after transplantation (median 3 m, range 0.3-8.8), with typical aHUS features: rapid GFR loss and laboratory signs of TMA. Eight patients presented late (median 46m, range 18-69) after transplantation. Of these, 3 patients showed typical aHUS features, while in 5 patients no laboratory evidence of TMA was seen, and only a gradual eGFR loss. Treatment with eculizumab resulted in disappearance of TMA and improvement/stabilization of eGFR in 14 patients. Withdrawal of eculizumab was thus far proposed in 10 patients, and successful in only 5. Median follow-up after recurrence was 29 months (range 3-53 months). At last follow-up median eGFR was 32.0 mL/min/1.73m² (range 7-80), considerably less than eGFR before recurrence (54.3 mL/min/1.73m², range 22-103).

Conclusions: Patients with aHUS who develop recurrence after kidney transplantation do not fully recover kidney function. The major cause is treatment delay due to late recognition of disease recurrence in patients who present with a “creeping creatinine”. Discontinuation of eculizumab is often unsuccessful.

PO1551
A Case of Thrombotic Microangiopathy from an Intra-Abdominal Abscess

Introduction: Infection mediated thrombotic microangiopathy (TMA) has a high mortality with many patients requiring kidney replacement therapy. Recognition of TMA secondary to infection in the setting of an intra-abdominal abscess is uncommon. We report a case of TMA from complicated diverticulitis and polymicrobial intra-abdominal abscess.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: A 25 year old non-vegetarian man presented with generalized abdominal pain, fatigue, chills and intermittent epistaxis. He was found to have severe acute renal failure with Coombs positive hemolytic anemia, thrombocytopenia, high fibrinogen, high PT/PTT, low ADAMTS13 activity (15%) and ADAMTS13 inhibitor. Further workup showed sigmoid diverticulitis with a large intra-abdominal and small intracranial mass culture positive for Streptococcus anginosus (an oral microbe with proclivity to abscess formation) and Escherichia coli. Shiga toxin was not tested. Kidney biopsy revealed acute TMA. Drainage of the abscess and treatment with antibiotics resolved the systemic features of TMA. Renal recovery was protracted and the patient required dialysis for three months, with a last sCr of ~2mg/dl.

Discussion: Infection mediated TMA is an important third subgroup of thrombotic microangiopathy. The mechanism of injury is likely due to the concerted effort of both bacteria. Escherichia coli produced shiga toxin causes direct damage to the endothelial cells, whereas the incorporation of non-human sialic acid from dairy and meat increased toxin affinity to endothelial cells and injury. S. anginosus produces an exotoxin that can lyse erythrocytes and platelets allowing IgM binding to the exposed Tn antigen, leading to the coombs positivity observed. There is decreased hepatic synthesis of ADAMTS13 in sepsis, and ADAMTS13 autoantibodies are reported in E. coli mediated TMA. Given high fatality rate, prompt recognition and treatment of the underlying infection is pivotal as ongoing infection propagates microangiopathy. Severe features of TMA can develop during the clinical course necessitating intensive treatments such as plasmapheresis. As infection can be a frequent trigger of TMA among patients with complement abnormalities, patients should undergo genetic testing of the regulatory genes involved in the complement system.

PO1552
Characteristics and Outcomes of Immune-Complex Membranoproliferative Glomerulonephritis and C3 Glomerulonephritis in Japan: A Retrospective Analysis of Data from the Japan Renal Biopsy Registry
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Background: The reclassification of membranoproliferative glomerulonephritis (MPGN) into immune-complex mediated MPGN (IC-MPGN) and C3 glomerulopathy (C3G) based on immunofluorescence findings in kidney biopsies has provided insights into two distinct diseases. C3G is further classified into dense deposit disease and C3 glomerulonephritis based on electron microscopic findings. Although these diseases have poor outcomes, limited Japanese literature confined to small, single-center cohorts exist on these diseases.

Methods: We retrospectively analyzed 81 patients with MPGN type I and III from 15 hospitals in the Japan Renal Biopsy Registry (J-RBR) to compare demographic, clinical characteristics and treatment outcomes of patients with IC-MPGN to those with C3G.

Results: Of the 81 patients reviewed by immunofluorescence findings in kidney biopsies, 67 patients had IC-MPGN and 14 patients had C3G. Age at diagnosis, systolic and diastolic pressures, proteinuria, impaired renal function, and hypoalbuminemia were significantly higher in patients with IC-MPGN than in those with C3G. About 80% of the patients in both groups were treated with immunosuppressive therapy. At last follow-up (median 4.8 years), complete remission rate of proteinuria was significantly higher in patients with IC-MPGN (64.3%) than in those with C3G (29.9%; P = 0.015). The renal survival rate was lower in patients with IC-MPGN when compared to C3G (73.1% vs. 100%; log-rank, P = 0.031). Systolic blood pressure and renal function at baseline were independent predictors of progression to end-stage kidney disease.

Conclusions: The overall prognosis of patients with C3G is more favorable than for patients with IC-MPGN.

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PO1553
Early Recurrence of C3 Glomerulopathy (C3G) in the Allograft

Background: C3G encompasses both C3 glomerulonephritis (C3GN) and Dense Deposit Disease (DDD), a rare group of kidney diseases associated with alternative complement pathway dysregulation that commonly recurs in the allograft. How early recurrence occurs is underexplored.

Methods: We reviewed cases of recurrent C3G in the allograft at CUIMC. Protocol biopsies were encouraged for transplanted C3G patients (PTS) at 6 months if a for-cause biopsy (bx) had not already been performed. Median (range) reported.

Results: 9 pts (13 F; 6 C3GN, 3 DDD) were included (Table 1). 6 PTS (46%) had previous allografts fail due to C3G recurrence. Age at transplant was 32 years (18-71). Time from transplant to histologic recurrence was 54 days (5-472). 4 PTS (31%) had bland urine at first recurrence. 7 PTS (54%) had histologic recurrence at first allograft bx, 15-18 months after transplant. After 2.3 years (0.33-10.1), 11 PTS (85%) remained with functioning allografts; 5 PTS (46%) had creatinine > 2 mg/dl. 2 DDD PTS had allograft failure. 6 PTS (43%) had acute T cell mediated rejection. 2 PTS received eculizumab-both were without clinical recurrence.

Conclusions: This series highlights earlier histologic recurrence of C3G in the allograft than previously reported, partly due to protocol bx. Many PTS were without urinary abnormalities. At last follow up, majority of PTS had significant transplant CKD, severe hypertension, proteinuria, and complement abnormality. Future study is needed to better understand if early detection of recurrence, coupled with anti-complement therapies, improves outcomes.

Summary of Clinicopathologic Course After Histologic Recurrence

PO1554
C3 Glomerulopathy in Children and Adolescents
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Background: C3 glomerulopathy (C3G) has been classified as a glomerular complement mediated disease with predominant C3 deposits since a decade ago. Data regarding clinical course, treatment options and long term prognosis in children and adolescents is still scarce. The aim of the study was to retrospectively describe a single tertiary center’s experience with C3G in the pediatric population, and correlate presentation, pathology, complement findings, response to treatment and disease progression.

Methods: A retrospective cohort study. Patients presented with C3G by the age of 18 years compromised the study group. All cases underwent kidney biopsy at presentation. Repeated kidney biopsy was performed on a need basis, in native or transplanted kidneys.

Definition of C3G was based on the 2013 consensus guidelines. Patients underwent complement workup and genetic tests. Treatment regimen was not uniform.

Results: 17 patients were diagnosed with C3 glomerulopathy. Features of Dense deposit disease (DDD) were found in 8 patients, C3 glomerulonephritis in 6 patients. For 1 patient EM was not available. Mean age at diagnosis was 12.7 years (range 1.9 – 17.3). 6 girls and 11 boys. Median follow up 4.4 years (range 1.1-20.9). Treatment modalities ranged from ACE inhibitors and Angiotensin receptor blockers to corticosteroids, Mycophenolate Mofetil, Plasmapheresis, Rituximab and Eculizumab. Only 2 (12%) patients achieved complete remission. 4 (23%) patients reached end stage renal failure and had kidney transplantation. All of them had disease recurrence in the transplanted kidney. Complement workup was positive for C3 in 6 patients, C4NeF in 2 patients, C3NeF in 2 patients, factor H antibodies in 2 patients. Genetic testing was positive in one patient. Elevated creatinine at presentation, severe proteinuria, DDD in kidney biopsy–were correlated with worse prognosis.

Conclusions: Understanding the pathophysiology of C3G as a complement mediated disease has progressed during the past years. Still no guidelines exist regarding treatment and prognosis in the pediatric population. Our cohort presented a wide variability in disease course and presentation. Further understanding of the correlation between exact complement abnormality and C3G prognosis is warranted, especially now when new complement system blockers may become available.
Utilizing Pharmacokinetic Studies to Optimize Therapy in a Child with C3 Glomerulonephritis and Nephrotic Syndrome: A Precision Medicine Approach

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Introduction: C3 glomerulonephritis (C3GN) is caused by complement alternative pathway dysregulation, has no definitive treatment and is characterized by progression to ESRD. Terminal complement blockade has successfully been used especially in patients with elevated C5b-9 levels.

Case Description: We describe a 6 year old boy with C3GN, who presented with nephrotic syndrome, severe hypertension (4 anti-hypertensive medications) and acute kidney injury. Complement C3 level was 0.12 g/L (normal 0.8-1.5) with pos C3NeF and elevated C5b-9 levels (2135, normal <239ng/ml) with a urine protein to creatinine ratio of 7, and complement C3 level of 76 mg/dL. He was re-dosed with eculizumab (600 mg every 2 weeks) and azathioprine, and over the course of 6 months, his serum creatinine, proteinuria, and complement C3 levels returned to normal. After weaning the frequency of his eculizumab infusions, he experienced a flare of DDD 15 months later. We confirmed sub-therapeutic plasma concentrations of eculizumab as free eculizumab levels were low on day 7 (9, normal >99 ug/ml) and undetectable on days 10 and 14 post-infusion. Eculizumab frequency was subsequently increased to weekly with MPA-AUC guided adjustment of MMF dosing.

Discussion: Use of pharmacokinetic studies can aid in individualized eculizumab treatment in C3GN patients with ongoing proteinuria and who failed to respond to standard dosing.

Remission of C3 Glomerulonephritis with Rituximab

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Introduction: C3 glomerulonephritis (C3GN) is a rare form of glomerulonephritis. It is diagnosed primarily by kidney biopsy with immunofluorescence showing deposits of C3 along the basement membranes. It differs from dense deposit disease with absence of the pathognomonic deposits on electron microscopy (1). There are no randomized trials to guide therapeutic decisions. Spontaneous and treatment-associated complete remissions are rare.

Case Description: 69-year-old female with history of well controlled hypertension on amloidine was sent to hospital with elevated creatinine of 2.52 (unknown baseline) with positive ANA - 1:320 titer. Patient was asymptomatic with negative family history of kidney disease. She denied taking NSAIDS. Serum creatinine on admission was 3.05 mg/dL. Urinalysis showed numerous RBCs with 2 g of proteinuria in the 24-hour urine collection. P-ANCA was positive. All other pertinent serologies were negative including complement levels. C-ANCA, MPO, PR3. Renal ultrasound revealed medical renal disease. Renal biopsy was performed and preliminary reports showed crescentic glomerulonephritis. Pulse dose steroids was started followed by oral prednisone. In addition, Rituximab was started weekly. Final biopsy confirmed C3GN. Patient did not require dialysis and renal function significantly improved after 4 doses of rituximab to serum creatinine of 1.5 mg/dL.

Discussion: In C3GN with rapidly progressive glomerulonephritis (crescents on biopsy), treatment is not well established. Most patients are treated with steroids in combination with either cyclophosphamide or Mycophenolate mofetil (2). Rituximab was used in some case reports (3). In our patient, since P-ANCA was positive and preliminary biopsy showed crescents, Rituximab was started immediately after pulse dose steroids. Patient did not require dialysis, due to good response and remission. Rituximab is a promising treatment option for C3GN. Reference Smith, R.J.H., et al C3 glomerulopathy — understanding a rare complement-driven renal disease. Nat Rev Nephrol 15, 129–143 (2019). Fernando Caravaca-Fontán et al. Mycophenolate Mofetil in C3 Glomerulopathy, and Pathogenic Drivers of the Disease. Clin J Am Soc Nephrol. September 2020, 15 (9) 1287-1298. Giaine P et al. Remission of C3 glomerulopathy with rituximab as only immunosuppressive therapy. Clin Nephrol. 2015 Jan;83(1):57-60.

Myeloperoxidase Immunohistochemical Staining and Response to Eculizumab in a Pediatric Patient with Dense Deposit Disease


Introduction: Previous studies have demonstrated residual complement mediated deposits in repeat renal biopsies of patients with C3 glomerulonephropathies (Dense deposit disease (DDD) and C3 glomerulonephritis) following eculizumab treatment despite clinical improvement. With the residual complement deposition, it is often difficult to determine whether there is a reduced complement mediated endothelial cell injury. Herein, we report the use of myeloperoxidase (MPO) immunohistochemical staining to show decreased glomerular endothelial cell injury in a pediatric patient with DDD on chronic eculizumab therapy.

Case Description: Our patient was diagnosed with DDD by renal biopsy when he was 5 years old after presenting with a serum creatinine of 5.2 mg/dL, a urine protein to creatinine ratio of 2.5, and a complement C3 level of 50 mg/dL. Functional complement testing showed the presence of C3 and C5 nephritic factors. He was treated with eculizumab (600 mg every 2 weeks) and azathioprine, and over the course of 6 months, his serum creatinine, proteinuria, and complement C3 levels returned to normal. After weaning the frequency of his eculizumab infusions, he experienced a flare of DDD 15 months after initial presentation with a serum creatinine of 3.6 mg/dL, urine protein to creatinine ratio of 7, and complement C3 level of 76 mg/dL. He was re-dosed with eculizumab (600 mg every 2 weeks) with a rapid response to treatment. He had normalization of his serum creatinine to pre-flare levels within 6 months. Since then he has been maintained on eculizumab infusions (600 mg every 4 weeks) along with mycophenolate mofetil. A second kidney biopsy was performed after 3 years of treatment with eculizumab to evaluate response to treatment. The biopsy showed some residual features of dense deposit disease including C3 complement deposition. To evaluate if eculizumab blocked complement mediated injury on glomerular endothelial cells, MPO staining of his initial and repeat biopsy was performed: his initial biopsy revealed diffuse endothelial staining for MPO along glomerular endothelium and the repeat biopsy showed either no MPO staining or weak MPO staining in the glomerular endothelium.

Discussion: In this case, we find that MPO immunohistochemical staining may be useful for monitoring the response to complement blockade in patients with DDD.
PO1558

Pregnancy-Associated Membranoproliferative Glomerulonephritis (MPGN)

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Introduction: Nephrotic syndrome (NS) in pregnancy is rarely due to MPGN. We present a case of MPGN in pregnancy for which no other cause was found.

Case Description: A 33-year-old G1P0 woman develops hypertension and proteinuria at 12 weeks gestation followed at 21 weeks by NS (75 g/24h proteinuria, albumin 1.1 g/dL), AKI with creatinine (Cr) 1.1 mg/dL (up from 0.6), hematuria, and mildly elevated AST and ALT. C4 is low (5.9 mg/dL). SPEP and UPEP detect monoclonal IgG kappa with serum light chain ratio 5.1. ANA, anti-dDNA, cryoglobulins, C3 nephritic factor, and serologies for hepatitis B and C, T. pallidum, and HIV are negative. Renal failure (B) reveals MPGN. After counseling, she opts to end the pregnancy. Cr, AST, ALT, and hematuria rapidly normalize, but the proteinuria at first persists. Immunosuppression is offered, but she declines. The proteinuria slowly falls to <0.7 g Cr with supportive care and telmisartan over a year. Apart from low C4, an atypical hemolytic uremic syndrome (aHUS) panel is negative. Genetic testing for aHUS is also negative (heterozygous mutation in DFGK and heterozygous deletion in CFH R1-CFH R3). HLA analysis shows B35 and B51 alleles. C4d staining later performed on the biopsy is strongly positive.

Discussion: As in this case, NS in pregnancy is associated with an increased risk of complications such as superimposed preeclampsia. The etiology of this MPGN case is unknown, with no clear infectious or autoimmune cause. The C4d deposition and negative aHUS testing suggest a defect in the classic complement pathway. This paraprotein may or may not be involved as, though the immune complex deposition was polyclonal, monoclonal IgG-kappa has been rarely reported to activate complement in other autoimmune disorders. Regardless of mechanism, we speculate this MPGN case was triggered by pregnancy as it improved after the pregnancy with supportive care alone.

PO1559

Comparing and Contrasting Glomerular Disease Patients: A Real-World Analysis Showing Demographic, Clinical, and Treatment Differences Across More Than 1,000 Patients

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Background: One-half of nephrologists selected glomerular diseases as their leading area of interest in nephrology in 2020. These rare and often-idiopathic disorders are seen as particularly challenging to manage, but an influx of promising pipeline drugs may offer new treatment options in the not-so-distant future.

Methods: 1,112 glomerular disease patient records were collected in collaboration with 290 US nephrologists via HIPAA-compliant, online chart review tool between December 20, 2020 – February 16, 2021.

Results: Chart audits reveal ~8% of nephrologists’ patient populations have a glomerular disorder. Of that group, 26% have IgAN, 26% have FSGS, and 3% have Alport’s Syndrome, among other conditions. IgAN patients are typically middle-aged, white males, in the middle-to-upper class and often present with hypertension, hyperlipidemia, and/or obesity. FSGS patients are mostly middle-aged, black males, in the lower-to-middle class and often present with hypertension, hyperlipidemia, obesity, and/or edema. Alport Syndrome patients tend to be younger (18-49), white males, in the lower-to-middle class and present with hypertension, hearing loss, and sometimes ocular abnormalities. Of the three conditions, FSGS patients most heavily prescribed steroids and advanced therapies like MMF, cyclophosphamide, and Achar Gel and are least likely to be deemed “optimally managed” by their nephrologist. Alport patients are much less likely to receive steroids and are most likely to be seen as optimally managed. Interestingly, despite the value of ACEI/ARB therapy, 42% of IgAN patients were not on therapy at referral, with FSGS and Alport close behind. Nephrologists are trialing SOLITZis across conditions, with up to one-in-ten patients currently on the drug. A diagnosis for Alport Syndrome may take several months or even years after referral to determine (unlike IgAN and FSGS where it usually takes under four months). Alport is also the least likely of the three diseases to be diagnosed via kidney biopsy. Patient referrals are often deemed “late” by nephrologists, but particularly with the faster-progressing FSGS and IgAN.

Conclusions: Deeper understanding of key comparative differences among rare glomerular diseases may aid physicians in developing strategies for diagnosis and treatment.

PO1560

Glomerular Diseases in Flanders: Overview of the FCWG Biopsy Registry

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Background: High-quality population-based registries on glomerular diseases are required for epidemiological study and new trial design. The FCWG (Flemish Collaborative Glomerulonephritis Group) database is a population-based registry that has been including data on all native kidney biopsies performed in Flanders since 2017 (Northern part of Belgium) covering a population of approximately 6.5 million inhabitants.

Methods: Clinical data and pathological diagnosis according to the ERA-EDTA Coding system for Primary Renal Disease are collected together with pathological data including primary and secondary pathological diagnoses according to the Mayo Clinic/Renal Pathology Society Consensus Guideline 2016. Here, we describe the main results of the first three years of the registry.

Results: From 2017 until 2019, 2178 biopsies were included, of which 5.7% were performed in the pediatric population. Median age (IQR) was 59 years (42-71). Biopsy incidence proportion was 1.30 biopsies p.m.p. per year in the adult population. Glomerular disease was present in 54% of the adult biopsies (Fig. 1A). IgA-nephropathy (IgAN) was the most frequently diagnosed disease in adults (17.3% of total, 30.2% of glomerular subcategory). The etiologies of the nephrotic syndrome differed across age categories, with membranous nephropathy (MN) being most frequently diagnosed in the total group of adult nephrotic patients (Fig. 1B). IgAN and pauci-immune glomerulonephritis (AAS) were the two most important causes of the nephritic syndrome in adults. A crescentic pattern of injury was most frequently diagnosed in adults with AAV, lupus nephritis (LN) and IgAN (Fig. 1C, crescents in 82%, 31% and 24% of biopsies, respectively).

Conclusions: The FCWG database is a valuable population-based registry that characterizes the epidemiology of glomerular disease in Flanders. These results are relevant to the clinician, will enable disease subgroup analyses and are useful to set up observational or interventional trials in patients with glomerular disease.
PO1562
The Thromboembolism Among Hospitalized Patients with Different Types of Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital
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Background: Chronic kidney disease is associated with hypercoagulability and platelet dysfunction. However, data on thromboembolism associating different types of chronic glomerulonephritis (CGN) are less.

Methods: We conducted a retrospective analysis using the database of hospitalization with CGN in Peking Union Medical College Hospital (PUMCH), China from 2000 through 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify types of thromboembolism and glomerulonephritis including lupus nephritis (LN), systemic vasculitis (AAV), Henoch-Schönlein purpura nephritis (HSPN), IgA nephritis (IgAN), idiopathic membranous nephropathy (IMN), minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Cochran-Armitage trend and Logistic regression were used in the analysis.

Results: Between 2000 and 2017, there were 15,714 hospitalizations with the aforementioned CGN. Their mean age was 51.7±19.8 years and 39.4% were males. The annual prevalence of overall thromboembolism increased steadily from 1.6% in 2000 to 6.6% in 2017 in a dose-response manner (p for trend <0.001). Among all thromboembolism cases, 49.8% had venous thromboembolism and 31.7% had a pulmonary embolism. The prevalence of thromboembolism in IgAN, FSGS, MCD, IMN, HSPN, LN, and AAV were 0.6%, 2.4%, 2.6%, 5.89%, 2.2%, 4.4%, and 5.3%, respectively. The patients with thromboembolism had a 2.30-fold increased risk of death (95%CI 1.53-3.40) after adjustment for age and gender. In multivariate analyses adjusted for multiple confounders such as gender, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, infection, LN (OR 8.15; 95% CI 5.25-12.65), IMN (OR 6.93; 95% CI 4.39-10.92), AAV (OR 4.53; 95% CI 2.66-7.61), MCD (OR 4.42; 95% CI 2.56-7.61), HSPN (OR 4.05; 95% CI 2.33-7.03), and FSGS (OR 3.18; 95% CI 1.56-6.49) were significantly associated with the increased risk of thromboembolism compared with IgAN.

Conclusions: In the present study, chronic glomerulonephritis, particularly lupus nephritis, idiopathic membranous nephropathy, and systemic vasculitis were independently associated with an increased risk of thromboembolism.

PO1563
Identification and Validation of Infection-Related Acute Care Events in Patients with Glomerular Disease
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Background: Infections are an important contributor to morbidity and mortality in glomerular disease (GD). Accurate identification of infections using real world clinical data would support the conduct of observational studies examining infection risk, but standard approaches are labor-intensive. We sought to derive and test the validity of diagnosis-code based algorithms to identify infection-related acute care events (ACEs) within a large cohort of children and adults with GD.

Methods: CureGN is a prospective multi-center cohort study of patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, or IgA Nephropathy. We describe the sensitivity, specificity, and positive and negative predictive values (PPV/NPV) of four infection diagnosis code lists using manually curated infectious and non-infectious ACEs (hospitalization or emergency department visit) as the gold standard. We then validate the best performing code list within a more contemporary CureGN cohort, using multi-site adjudication of medical records.

Results: In the development phase, the optimal performing combination of diagnosis code lists were used by CureGN coordinators combined with those described by Sahil et al. (PPV 78%, 95% CI 73-83%) (Table 1). Using this code list, 265 infections and 1231 non-infectious ACEs were identified among 2599 CureGN participants in the validation phase, of which 124 were randomly selected and adjudicated. The PPV and NPV for the final code set were 87% (95% CI: 75-99%) and 83% (95% CI: 72-93%) respectively.

Conclusions: Diagnosis codes can be used to accurately identify infection-related ACEs among patients with GD. Future studies should validate our findings in other GD cohorts and for specific infection types of high-severity or burden.

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PO1564
Patients with Glomerular Disease Are at Very High Risk of TB Infection Compared to the General Population
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Background: Advanced kidney disease is a known risk factor for active TB disease; however this risk has not been studied in patients with glomerular disease (GN). We sought to determine the incidence of TB disease in patients with GN and to explore the risk of TB disease associated with immunosuppression in patients with GN.

Methods: A population-level cohort was created using a centralized kidney registry (2000-2012) of all GN cases in British Columbia, Canada: IgA nephropathy (IgAN) n=857, focal segmental glomerulosclerosis (FSGS) n=564, ANCA-GN n=404, lupus nephritis (LN) n=360, membranous nephropathy (MN) n=398, minimal change disease (MCD) n=191, and other GN (n=305). TB disease was ascertained by linkage to administrative databases. High TB incidence was defined as >30 per 100,000 person years (PY) consistent with the definition used in first-world countries. Incidence rates were standardized to the general population to generate standardized incidence ratios (SIR, 95% CI). Hazard ratios were calculated using Cox proportional hazards regression.

Results: During a median follow-up 6.2 years, there were 41 cases of TB disease. TB incidence rate was 197.4/100,000PY, and was higher in patients with LN vs. other types of GN (403.0/100,000PY, p<0.05). TB incidence in patients with GN was 23-fold higher than the general population (SIR 23.4, 16.8-31.7), and was high in both Canadian and foreign-born patients (range 124.1-579.6/100,000PY). TB incidence was higher during periods of IS use (282.4 vs. 147.8 per 100,000PY, p<0.05), and most cases (80.5%) had IS exposure prior to TB diagnosis. Time from IS to TB disease was highly variable, with median 3.9 years but 24% of TB cases occurred within 1 year. Reduced kidney function and higher proteinuria were also associated with increased TB risk (Table).

Conclusions: Patients with GN have a high risk of TB disease, irrespective of GN type or country of origin. TB disease can occur within months of starting IS, suggesting that all GN patients should be screened for latent TB early in their disease course.
PO1565
The Impact of Obesity on Glomerulonephritis: A Multicenter Cohort Study of Kidney Biopsy over 40 Years
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Background: Worldwide obesity has increased by almost three times between 1975 and 2020. Many studies reported that obesity related kidney disease was also increasing, and most of them were focal segmental glomerulosclerosis (FSGS). However, little was known about the prevalence and outcome of other type of glomerulonephritis (GN) in obese patients.

Methods: A total of 14,833 adult patients who underwent kidney biopsy and had body mass index (BMI) were identified in 18 tertiary hospitals during 1979-2018. Obesity was defined as BMI ≥ 30 kg/m². We analyzed the prevalence of specific forms of glomerulonephritis in obese patients and effect of obesity on mortality and end stage kidney disease (ESKD).

Results: Obese patients in glomerular disease have increased about 12.8-fold over 40 years between 1979-1988 (0.6%) and 2009-2018 (7.7%). In GN patients with obesity, prevalence of IgA nephropathy (IgAN) is the most common (33.7%) followed by FSGS (13.3%), minimal change disease (MCD) (10.8%), membranoproliferative (MPGN) (10.6%), diabetic nephropathy (DMN) (6.0%), lupus nephritis (LN) (2.7%), and hypertensive nephropathy (HT-N) (2.6%). The prevalence of FSGS (HR 1.60, 95% CI 1.24-2.06), DMN (HR 1.46, 95% CI 1.01-2.12) and HT-N (HR 2.14, 95% CI 1.29-3.54) were significant higher in obese patients compared than non-obese patients. Obesity had a 1.39-fold increased risk for ESKD progression during 93.8 ± 13.3% months follow up in total patients (95% CI 1.11-1.73). Obesity had higher risks for progression of ESKD in MCD (HR 2.48, 95% CI 1.02-6.04) and LN (HR, 3.28, 95% CI 1.30-8.31). In patients with FSGS, DMN, and HT-N, obesity was not associated with ESKD. Obesity was not associated with mortality in GN patients although obesity was related to mortality only in MCD patients (HR 2.48, 95% CI 1.02-6.04).

Conclusions: Obesity rates are increasing in GN patients. The prevalence of FSGS, DMN, and HT-N are significantly higher in obese patients although IgAN is the most common form of GN. Obesity had significant risks for progression of ESKD in patients with GN, especially MCD and LN patients.

PO1566
Obesity at Time of Diagnosis Is Associated with Proteinuria in Glomerular Disease
Evan Zeijler, Yichun Hu, Caroline J. Poulton, Lauren N. Blazek, Amy K. Mottl, Jennifer E. Flythe, Susan L. Hogan. UNC Kidney Center, Chapel Hill, NC.

Background: Obesity is an established risk factor for chronic kidney disease (CKD). The relationship between obesity and glomerular disease outcomes is not well studied.

Methods: We evaluated a cohort of adult patients with biopsy-proven IgA nephropathy, focal segmental glomerulosclerosis (FSGS), ANCA-associated vasculitis (ANCA), or membranoproliferative (MPN) between January 2014 and June 2020, and follow up through April 2021. We categorized body mass index (BMI) at time of biopsy as BMI<25 kg/m², 25 kg/m²≤BMI<30 kg/m² or ≥30 kg/m². We used Fisher's exact and Kruskal-Wallis tests to compare baseline characteristics between groups and a proportional hazards model to evaluate factors associated with CKD progression to kidney replacement therapy (KRT).

Results: The cohort included 153 patients: 77 (50%) male with median age 50 (IQR 38-65) years and median BMI 28 (IQR 24-34) kg/m². Compared to patients with lower BMIs, patients with BMI ≥25 kg/m² had higher median urine protein to creatinine ratios (uPCR) (p=0.02, Table 1). In univariate analyses, factors associated with progression to KRT were: blood pressure (p = 0.01), uPCR (p <0.01), and lower eGFR (p=0.001). BMI at biopsy was not associated with CKD progression, adjusted HRs (95% CIs): BMI 25-29.9 kg/m² ≤ 1.09 (0.42-2.83); BMI ≥ 30 kg/m² ≤ 1.54 (0.68-3.52). Logrank PC-value for KM curves was 0.004, with paired uPCR values imparting the greatest distinction between curves (data not shown).

Conclusions: Among glomerular disease patients, BMI was associated with proteinuria, but not with progression to KRT.

Funding: NIDDK Support

PO1567
When to Biopsy Type 2 Diabetes Mellitus (DM2)
Haridjan Sosa Barrios,1,2 Victor Burguera,1,2 Maria Garcia,1,2 Ana Saiz,1,2 Javier Villacortaperez,1,2,3 Guillermo F. Conde,1,2 Milagros Fernández-Lucas,1,2 Maite Rivera Gorria,1,2 1Hospital Universitario Ramon y Cajal, Madrid, Spain; 2Instituto Ramon y Cajal de Investigacion Sanitaria, Madrid, Spain; 3Universidad de Alcala de Henares Facultad de Medicina y Ciencias de la Salud, Alcala de Henares, Spain.

Background: DM2 patients may have diabetic (DN) or non-diabetic renal disease (NDRD) and a histological diagnosis is needed. There is no clear consensus on when to biopsy, but a predictive model was recently published (1).

Methods: Aim: Assess NDRD prevalence, histology and apply the predictive score in our cohort. Methods: Retrospective analysis of native kidney (NK) biopsies performed in our center from 2016 to 2020. Data collected included DM history, retinopathy, peripheral vascular disease (PVD), insulin prescription, proteinuria, BMI and hematuria >10 cells/HPF. A score ≥3 was highly suggestive of DN and would preclude renal biopsy (RB). Results: 62 of 274 NK RB’s had DM, 66.1% males with a mean age of 64±13.7 (range 23-83). Mean estimated glomerular filtration rate (MDRD4) was 41±26.5 ml/min/1.73m² (range 6-98) with mean BMI 27.9 (range 18-41). Mean proteinuria was 4453 mg/g (range 4.56249) and 51.6% had microhematuria. 51.6% had a DM history >10 and 28.3% < 5 years since diagnosis. 82.3% did not have retinopathy, 11.3% had neuropathy and 48.4% were on insulin. 27.4% had PVD, 6.5 % ischaemic cardiomyopathy (ICD) and 3 had a previous stroke. RB indications: 21 nephrotic syndrome, 2 nephritic syndrome, 6 proteinuria-hematuria, 18 non-nephrotic proteinuria, 7 renal impairment and 8 AKI. Histology: 22 had DN (38.6%), 35 NDRD (61.4%) and insufficient in 5. NDRD included crescentic glomerulonephritis, membranous, FSGS, chronic tubulointerstitial nephritis, ATN, IgA GN, minimal change, amyloid, hiperfiltration, glomerular sclerosis and chronic inespecific lesions. Longstanding DM (>10 y), retinopathy, neuropathy and PVD were independent predictors of DN (p value 0.02, 0.01, 0.001 and 0.001). Neither hematuria, nephrotic range proteinuria nor ICD were significant. Score: Patients with a score>3 had DN except 2 (oxalate crystals and cast nephropathy). 70.2% with a score>3 had NDRD and 64% of those with <1 did not have DN.

Conclusions: Excellent correlation with DN and could be efficient on RB decision making process in these patients. Validation in multicentric studies is desirable. 1.García-Martín F. et al. When to perform renal biopsy in patients with type 2 diabetes mellitus? Predictive model of non-diabetic renal disease. 10.1016/j nefro.2019.07.005

PO1568
Year of Life Lost due to Premature Death from Glomerulonephritis in Thailand
Chitnamorn Janphrang, Suchin Worawichwong, Sarinya Boongird, Umaporn Udomsubpayakul, Montira Assanatham, Chagriya Kitiyakara. Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.

Background: The contribution of Glomerulonephritis (GN) on mortality is not fully known. The impact of each GN subtype on premature mortality can be measured by calculating the year of life lost (YLL), which takes into account the age at which deaths occur. Therefore, this study aimed to estimate premature mortality in GN using the average YLL.

Baseline Characteristics Across BMI Groups

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 (36-45)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 (25-30)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: A total of 1,022 kidney biopsies was performed. The median follow-up time was 67 (IQR 45, 92) months. Age for GN patients was 43.9 ± 16.7 years and 44.8% males. The total and average YLL of all GN were 4741.9 years and 4.6 years, respectively. The average YLL for secondary GN (n = 391) was higher than primary GN (n = 469) being 7.31 vs 2.23 years (p < 0.05). DN (n = 97) had average YLL at 9.76 years followed by LN (n = 243) at 7.1 years. The average YLL (years) for primary GN were: FSGS (n=125), 2.52 years; MGN (n=106), 2.32; IgAN (n=164), 2.26; and MCD (n=74) 1.57.

Conclusions: GN causes premature mortality with secondary GN being associated with higher premature death than primary GN. DN and LN nephritis have the highest YLL. This study provides useful information on the impact of GN for prioritization of public health policies intervention.

PO1569
The Significance of Hematuria in Primary Proteinuric Glomerular Disease Outcomes
Dorota Marchel,1 Maria Larkina,1 Damien Ferman,1 Jennifer Lai Yee,1 Debbie S. Gipson,1 Andrew S. Bomback,2 Pietro A. Canetta,2 Amy K. Mottl,2 Rulan S. Parekh,3 Manish K. Saha,3 Matt G. Sampson,3 Howard Trachman,3 Richard A. Lafayette,4 Laura H. Mariani,1 University of Michigan, Ann Arbor, MI; Columbia University, New York, NY; University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; Boston Children’s Hospital, Boston, MA; NYU Langone Health, New York, NY; The Hospital for Sick Children, Toronto, ON, Canada; Stanford University, Stanford, CA.

Background: Hematuria is associated with the incidence and progression of CKD. The study aims were to assess the prevalence of hematuria in a large cohort of proteinuric glomerular disease and assess the association between hematuria and kidney-related outcomes.

Methods: Hematuria was assessed at first reported study urinalysis in patients with MN, MCD, and FSGS in NEPTUNE and CureGN cohorts with >24 months of follow-up. Hematuria was defined as small, moderate, or large blood on urinary dipstick and no hematuria was negative or trace blood. Multivariable Cox proportional hazards models were fit for time to composite outcome (ESKD or 40% decline in GFR and eGFR <60) and proteinuria remission (UPCR <0.3 mg/g).

Results: 1,108 adults and children were included. 412 (37%) patients had FSGS, 389 (36%) had MCD, and 307 (28%) had MN. 745 (67%) participants were positive for hematuria at first urinalysis. Those who had hematuria vs. those without at first urinalysis were more likely to have an underlying diagnosis of MN (37% vs 23%), be older (34 vs 25 years), have shorter time since biopsy (128 vs 315 days) and higher UPCR (3.6 vs 8.0). Patients with hematuria had higher rates of the composite outcome and lower rates of complete remission (Figure 1). After adjusting for diagnosis, age, sex, UPCR, eGFR, time since biopsy, and cohort, hematuria was associated with a higher hazard of reaching the composite outcome (HR 1.39 [1.05, 1.84], p-value 0.02) and lower hazard of reaching proteinuria remission (HR 0.71 [0.55-0.91], p-value 0.006).

Conclusions: Hematuria is prevalent among patients with podocytopathic disease not classically considered nephritic. There was an independent association between hematuria and worse kidney related outcomes. The underlying mechanisms warrants further investigation and include genetic predisposition, structural alterations in the glomerular basement membrane, and tubular toxicity from heme pigment.

Funding: NIDDK Support, Other NIH Support - NCATS

PO1570
Vacularised Denatured Casts Are a Distinct Type of Urinary Cysts Associated with Severe Nephrotic Glomerulopathy
Akanaskh Ramandan,1,2 José A. Poloni,3 Abhirup Sarkar,3 Ana P. Giolo Franz,4 Juan Carlos Q. Veloz,1 3 Ochsner Medical Center - New Orleans, New Orleans, LA, 4Universidade do Vale do Rio dos Sinos, Sao Leopoldo, Brazil, 5Suraksha Diagnostics, Kolkata, India; *Hospital de Clinicas de Passo Fundo, Passo Fundo, Brazil.

Background: Urinary casts identified through microscopic examination of the urinary sediment (MicrExUrSed) constitute clinically useful elements for the diagnosis of acute and chronic kidney pathologies. Granular, waxy and cellular casts are well characterized. However, a unique type of casts containing non-polarizable lipid-like granules immersed within a lightly granular cast matrix is occasionally found. These casts have been labeled as vacuolated denatured casts (VDC).

Methods: We utilized an educational social media platform (Twitter) to probe for individual cases of VDC. We surveyed known educators who frequently post microphotographs of MicrExUrSed asking for filed cases of identification of VDC. Demographic and clinical characteristics were extracted and representative images were compiled for correct identification of VDC.

Results: Four urine microscopists (2 from South America, 1 from India, 1 from USA) contributed to the case series. A total of 12 cases were identified. Images were carefully reviewed to confirm identity of VDC. Median age 53 (27-78), 80% men, 50% had type 2 diabetes mellitus. Median serum creatinine at the time of MicrExUrSed was 3.6 (1.7-5.5) mg/dl. All (100%) patients had >3 protein by urine dipstick. Urine protein-creatinine ratio was in the nephrotic range in all 5 cases with available value (median 10.2 [3.3-11.8] g/g). Concomitant findings included hematuria (58%), waxy casts (67%), granular casts (80%), fatty casts (42%) and renal tubular epithelial cells (58%). Histopathological diagnosis was available in 10 cases: 3 diabetic glomerulopathy, 3 focal segmental glomerulosclerosis, 2 transplant glomerulopathy, 1 membranous nephropathy and 1 advanced arterio nephrosclerosis. Greater than 25% interstitial fibrosis was present in 6/10 (60%) cases.

Conclusions: VDC are a distinct type of casts that can be found in specimens of patients with advanced proteinic glomerulopathy. The specific origin and composition of these casts remains unknown and requires further study.

PO1571
Detection of Urinary Acanthocytes for the Diagnosis of Glomerulonephritis
Akanaskh Ramandan,1,2 Sweeta Rani Kanduri,1 Vinip Varghese,1 Sarah P. Rosenbloom,1 Juan Carlos Q. Veloz,1,3 Ochsner Medical Center - New Orleans, New Orleans, LA; The University of Queensland Ochsner Clinical School New Orleans, New Orleans, LA.

Background: Acanthocyturia is a specific indicator of glomerulonephritis (GN). However, it is reported that the sensitivity of acanthocyturia for the diagnosis of GN is merely around 50%. Examiner expertise is expected to affect the ability to identify urinary acanthocytes. Thus, we hypothesized that in a well-equipped laboratory with proficient observers, the sensitivity of acanthocyturia for the diagnosis of GN can be improved.

Methods: In our institution, we have established a prospective data collection of individuals seen in nephrology consultation who had urine specimen subjected to microscopic examination (MicrExUrSed) as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed within 2 weeks of the MicrExUrSed. We assessed the performance of acanthocyturia in the diagnosis of biopsy-proven GN. Acanthocyturia reflects glomerular hematuria caused by forms of glomerular disease characterized by injury to the endothelium, mesangium, glomerular basement membrane or blood vessel, but not injury to the podocyte that classically presents with proteinuria. Therefore, podocytocytic casts were grouped with other diagnoses (tubular, interstitial, etc.) as non-GN.

Results: Among 390 patients with MicrExUrSed, 70 underwent kidney biopsy and were included. Mean age was 55 years, 50% were women. White race accounted for 52% (median 16.7 years and 44.8% males). The total and average YLL of all GN were 4741.9 years and 4.6 years, respectively. The average YLL for secondary GN (n = 391) was higher than primary GN (n = 469) being 7.31 vs 2.23 years (p < 0.05). DN (n = 97) had average YLL at 9.76 years followed by LN (n = 243) at 7.1 years. The average YLL (years) for primary GN were: FSGS (n=125), 2.52 years; MGN (n=106), 2.32; IgAN (n=164), 2.26; and MCD (n=74) 1.57.

Conclusions: GN causes premature mortality with secondary GN being associated with higher premature death than primary GN. DN and LN nephritis have the highest YLL. This study provides useful information on the impact of GN for prioritization of public health policies intervention.

Funding: NIDDK Support, Other NIH Support - NCATS
PO1572
Feasibility and Acceptability of Home Urinalysis Monitoring Using a Smartphone Application
Daniella Levy Erez, Hannah C. Derwick, Susan L. Furth, Lance S. Ballester, Jonah Mint, Stephanie Onuemu, Michelle Denburg, The Children's Hospital of Philadelphia, Philadelphia, PA; Schneider Children's Medical Center of Israel, Petah Tikva, Israel; Hebrew IO, Tel Aviv, Israel; Ben Gurion University Faculty of Health Sciences, Beer Sheva, Israel.

Background: Monitoring proteinuria in patients with kidney disease is of crucial importance given its implications for long term disease progression and clinical management. As part of efforts to encourage test adherence, leveraging technology to provide a clinical grade urine analysis result from a home test can greatly enhance the clinical experience for patients, caregivers and providers.

Methods: Children and young adults (5-21 yrs old) at a single pediatric center participated. Caregivers or patients (>12yrs) completed a brief survey and then received a home urinalysis kit by mail. The Healthy.io smartphone app uses advanced computer vision to assess the urinalysis dipstick using the smartphone camera. Families downloaded the app through a text message link and performed a home urine test followed by a survey about their experience. Urine results immediately appeared in the app for patients and accessed by the study team through a secure portal. Patient satisfaction was compared between the new app and current practice (home albustix or a urine sample brought to clinic) using Wilcoxon rank test with a p value <0.05. Free text responses were analyzed to identify themes related to the app experience.

Results: 103 children, 63 (61%) male, median age 10.9 yrs. (IQR 7.8-14.2) were enrolled. Primary diagnosis included: 47(46%) glomerular disease, 48 (47%) non-glomerular disease and 8 (8%) kidney transplant recipients. 101(98%) patients were satisfied with the smartphone app compared to 41(40%) patients who were satisfied with the current practice (p=0.0001. (Table 1) Patients’ free text comments were divided into themes in table 2.

Conclusions: The Healthy.io home testing app received very high rates of satisfaction among patients and caregivers compared to current practice and holds great potential to enhance patient-centered care.

Funding: Commercial Support - Healthy IO Company

Table 1: Patient satisfaction with current practice and Healthy.io home urinalysis smartphone app

<table>
<thead>
<tr>
<th>Satisfaction</th>
<th>Healthy.io</th>
<th>Current Practice</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Satisfied</td>
<td>91%</td>
<td>81%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Satisfied</td>
<td>6%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Very Dissatisfied</td>
<td>0%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Written comments regarding App use

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>“It was easy and convenient!”</td>
</tr>
<tr>
<td>“The app provided valuable information!”</td>
</tr>
</tbody>
</table>

PO1573
Proliferative Glomerulonephritis in a Patient with NK Cell Lymphocytosis
Hannah Angle, Jia Yi, Koyal Jain. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Introduction: Monoclonal gammapathy of renal significance (MGRS) occurs in patients with non-malignant lymphoproliferative disorders who present with kidney injury secondary to monoclonal immunoglobulin deposition. 1 We present a rare case of proliferative glomerulonephritis (PGN) likely due to NK cell lymphocytosis.

Case Description: A 57-year-old male with NK lymphocytosis and IHTN presented with progressively worsening oliguric renal failure (creatinine 1.1 to 6.2 mg/dL over 3 months) and elevated lambda free light chains (FLC) with a k/λ ratio of 0.06 (k=3.14, λ=52.58). Urine sediment showed numerous dysmorphic RBCs and granular casts. Renal biopsy (limited specimen) revealed PGN with polyclonal-IgG-dominant deposition and background of moderate interstitial fibrosis and tubular atrophy. Although obvious monoclonal lesions were absent and the PGN may have been coincidental, there was concern for a potential paraneoplastic GN induced by NK lymphocytosis or, less likely, MGRS. Thus, patient was treated with Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD). However, due to worsening kidney function patient was started on hemodialysis, hoping for potential renal recovery. Despite significant hematologic response (plasma cell burden <1%), chemotherapy was discontinued after 7 months due to lack of renal improvement and worsening medication side effects.

Discussion: This case suggests a potential rare cause of PGN with polyclonal-IgG-dominant deposition due to NK cell lymphocytosis. This is the first case to describe a potential association between them. Additionally, while the patient did have a hematologic response to the CyBorD, there was no renal recovery. Although the PGN may have been coincidental, CyBorD therapy should have had some effect while treating PGN. A potential of the disease resulting in end-stage kidney disease within 3 months in our patient. It also brings up the question of whether it was the presence of NK cell lymphocytosis that worsened the renal prognosis. Such cases are extremely difficult to treat and likely have a poor prognosis. Reference: Leung, N. The evaluation of monoclonal gammapathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammapathy Research Group. Nat Rev Nephrol 15, 45–59 (2019), https://doi.org/10.1038/s41581-018-0077-4

PO1574
A Sporadic Case of Fibronectin Glomerulopathy in Which Mass Spectrometry Was Indispensable for the Diagnosis
Takahisa Kunitomo, Takahisa Kawakami, Kiyotaka Nagahama, Satoru Hibino, Kazuhiro Fukuoka, Yosinori Komagata, Shinya Kaname. Kyorin University, Tokyo, Japan.

Introduction: Fibronectin glomerulopathy (FG) is an autosomal-dominant hereditary disease, which is caused by deposition of mutated fibronectin (FN). The immunostaining of FN is decisive for the diagnosis. We present a case of FG, in which FN was not detected with immunostaining and the detection of FN with mass spectrometry determined the diagnosis.

Case Description: A 60-year-old female with non-functional right kidney with calculi, 5-year history of proteinuria and 2-year history of hypertension presented with proteinuria and nephrotic edema. There was no family history of kidney diseases. Physical examination was significant for blood pressure of 176/98 mmHg and the edema. Laboratory test showed serum creatinine of 2.53 mg/dL, serum albumin of 2.3 g/L, urinary protein 5.8 g/day, and slight urinary glomerular RBCs. Anti-nuclear antibody, monoclonal protein, cryoglobulin, HCV, or hypocomplementemia was not detected. Open biopsy was performed. Light microscopy showed lobular glomeruli with mesangial expansion with PAS-positive material. Immunoglobulins, including k and λ, light chains, and complements were not detected. Electron microscopy showed massive mesangial deposits with fibrillar structure. However, Congo red staining and immunostaining of DNAJPB and fibronectin (IST-4 and IST-9) were all negative. Finally, the analysis of microdissected glomeruli with liquid chromatography/mass spectrometry (LC/MS) revealed abundance of FN, demonstrating the diagnosis of solitary FG.

Discussion: FG is caused by deposition of the soluble form of FN from serum, rather than the insoluble form produced by resident cells. Therefore, immunostaining with the monoclonal antibody IST-4, which can detect soluble FN, is usually positive in FG, while that with IST-9, which binds only to cellular FN, is negative. Although IST-9 staining was negative in the reported case, FN was detected with LC/MS. This might be due to a structural change of FN in the deposits, which hindered the binding of IST-4 antibody to FN. Furthermore, it was also confirmed that LC/MS is a powerful method to identify characteristics of unexplained glomerular deposits.

PO1575
To Treat or Not to Treat? Therapeutic Challenges in a Case of Advanced Renal Sarcoma
Catherine Larned, John S. Thurlow, Maura A. Watson. Walter Reed National Military Medical Center, Bethesda, MD.

Introduction: Use of potentially toxic therapy in patients with low chance of renal recovery is clinically challenging. Kidney biopsy with significant interstitial fibrosis and tubular atrophy (IFTA) and reduced estimated glomerular filtration rate (eGFR) suggests unlikely recovery. We describe a patient with advanced IFTA who recovered substantial kidney function with treatment.

Case Description: A 55-year-old man was diagnosed with pulmonary and renal sarcomas. Renal biopsy at diagnosis showed granulomatous interstitial nephritis with non-caseating granulomas and 20% IFTA. Prednisone was started but was discontinued by the patient for onerous side effects. Serum creatinine (Scr) stabilized at 1.5-1.8 mg/dL. He returned two years later with Scr=5.8 mg/dL (eGFR 12 mL/min/1.73m2). Urinalysis was within normal limits with 10 mg/dL phosphorus 4.0 mg/dL and intact PTH 200 pg/mL. He lacked pulmonary or systemic symptoms to merit empiric treatment, and he was hesitant to receive steroids due to prior side effects. Given new concurrent diagnosis of a granulomatous and sclerotic lesions, repeat renal biopsy was performed revealing moderate interstitial fibrosis and nonspecific chronic interstitial nephritis with 50% IFTA consistent with sarcomatoid sarcoma. Despite concern for lack of recoverable kidney function due to high chronicity and reduced eGFR, treatment with high-dose prednisone was started based on the unknown time course of recurrence in a relatively young active patient. Scr improved to 3.0-3.2 mg/dL (eGFR 25 mL/min/1.73m2). The patient continued to receive prednisone until full renal recovery was achieved. Despite resolution of IFTA, prednisone was tapered over 12 months. Prednisone was stopped 9 months after initiation due to lack of clinical improvement and prednisone side effects.


Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Clinicopathological Characteristics of Adult IgA Nephropathy: A Retrospective Cohort Study

Dawn J. Caster,¹ Clint Abner,² Kerime Ararat,³ Patrick D. Walker,² Amin Yakubu,⁴ Martin C. Bunke,⁴ ¹University of Louisville, Louisville, KY; ²Arkana Laboratories, Little Rock, AR; ³Genesis Research, LLC, Hoboken, NJ; ⁴Traverse Therapeutics Inc, San Diego, CA.

Background: IgA nephropathy (IgAN) is the most common form of primary glomerular nephropathy and a leading cause of chronic kidney disease (CKD). These analyses characterize clinical and histological features of IgAN in adults at time of kidney biopsy.

Methods: A retrospective study of clinical and histologic characteristics was performed in patients (pts) ≥18 yrs of age with ≥1 IgAN-positive kidney biopsy without prior kidney transplant reported from Arkana Laboratories (Jan 1, 2016-May 30, 2020). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation without race modifier. All results are at the time of biopsy.

Results: Of 67,262 kidney biopsies performed during the study period, 4,384 (6.5%) IgAN positive cases met the study criteria and were included, of which, 62.7% were male, 49.6% White, 5.1% African American, 5.3% Hispanic, 5.6% Asian and 34.4% Unknown/Other race/ethnicity. Mean (SD) age at biopsy was 47.7 (16.6) yrs. Urine protein to creatinine ratio/24-hour urine protein data were available for 52.4% of pts and the median (Q1-Q3) was 3.0 (1.0 – 5.0) g/g. Additionally, 65.2% of pts had hypertension, 63.1% had known hematuria, 25.7% had severe arteriosclerosis, 15.8% had severe arteriolosclerosis, and 49.6% had ESKD/death occurred in 53% of patients (<1% death). Kaplan-Meier survival curves of those without ESKD at baseline with renal diagnosis or symptom presentation. Patients were grouped into those with ESKD or negative notion. Patients without a record of renal biopsy, valid eGFR and proteinuria or negative notion. Patients without a record of renal biopsy, valid eGFR and proteinuria levels has not been well described in IgAN and is presented here.

Conclusions: The large proportion of pts diagnosed at CKD stage 3 and high MEST-C scores for S and T suggest significant disease duration at the time of biopsy. Earlier intervention may be of value to prevent ESKD.

Funding: Commercial Support - Traverse Therapeutics

Table 1. Immunofluorescence microscopy characteristics of adults with biopsy-confirmed IgA nephropathy

<table>
<thead>
<tr>
<th>IgA</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/Trace</td>
<td>806</td>
<td>20.9%</td>
</tr>
<tr>
<td>2+</td>
<td>200</td>
<td>5.3%</td>
</tr>
<tr>
<td>3+</td>
<td>238</td>
<td>6.0%</td>
</tr>
<tr>
<td>4+</td>
<td>120</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IgG</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/Trace</td>
<td>714</td>
<td>18.6%</td>
</tr>
<tr>
<td>2+</td>
<td>175</td>
<td>4.6%</td>
</tr>
<tr>
<td>3+</td>
<td>60</td>
<td>1.6%</td>
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<table>
<thead>
<tr>
<th>Cd</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/Trace</td>
<td>1,126</td>
<td>29.7%</td>
</tr>
<tr>
<td>2+</td>
<td>1,037</td>
<td>26.9%</td>
</tr>
<tr>
<td>3+</td>
<td>1,455</td>
<td>37.2%</td>
</tr>
<tr>
<td>4+</td>
<td>755</td>
<td>19.7%</td>
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<table>
<thead>
<tr>
<th>Mesangial Hypercellularity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant mesangial hypercellularity</td>
<td>2,210</td>
<td>57.2%</td>
</tr>
<tr>
<td>Mild to moderate mesangial hypercellularity</td>
<td>2,008</td>
<td>52.7%</td>
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<table>
<thead>
<tr>
<th>Endocapillary Hypercellularity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No endocapillary proliferation</td>
<td>3,640</td>
<td>83.0%</td>
</tr>
<tr>
<td>Mild endocapillary proliferation</td>
<td>744</td>
<td>17.0%</td>
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<table>
<thead>
<tr>
<th>Segmental Sclerosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of segmental sclerosis and/or adhesion of tuft to Bowman capsule</td>
<td>1,539</td>
<td>35.1%</td>
</tr>
<tr>
<td>Presence of segmental sclerosis and/or adhesion of tuft to Bowman capsule</td>
<td>2,245</td>
<td>64.9%</td>
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<table>
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<table>
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<td>15.5%</td>
</tr>
<tr>
<td>C2 (present in ≥25% or ≥25%</td>
<td>147</td>
<td>3.4%</td>
</tr>
</tbody>
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*May not equal 100% due to unknown values

Natural History of IgA Nephropathy: A Retrospective Cohort Study

Jonathan Barratt,¹ ² Moin Saleem,¹ Fiona E. Braddon,¹ Kevin Carroll,¹ Ping He,² Bruce M. Hendry,³ Alex Mercer,⁴ David Pitcher,⁴ Retha D. Steenkamp,¹ A. Neil Turner,¹ Daniel P. Gale,⁴ ¹University of Leicester, Leicester; United Kingdom; ²Leicester General Hospital, Leicester; United Kingdom; ³University of Bristol, Bristol, United Kingdom; ⁴Bristol Royal Hospital for Children, Bristol, United Kingdom; ⁵UK Renal Registry, Bristol, United Kingdom; ⁶The Renal Association, Bristol, United Kingdom; ⁷Royal Free Hospital, London, United Kingdom; ⁸University College London, London, United Kingdom; ⁹Traverse Therapeutics Inc, San Diego, CA; ¹¹JAMCO Pharma Consulting, Stockholm, Sweden; ¹²KJC Statistics Ltd, Cheshire, United Kingdom.

Background: Primary IgA nephropathy (IgAN) is the most common form of glomerulonephritis and a major cause of renal failure. Here we describe the natural history of IgAN using the UK National Registry of Rare Kidney Diseases (RaDaR). Since 2013, patients with biopsy-proven IgAN and eGFR <60 mL/min/1.73m² or proteinuria >1 g/24h have been enrolled into RaDaR from 107 adult and paediatric kidney units across the UK, including retrospective and prospective data. Patients with systemic vasculitis or pre-existing liver disease were excluded.

Methods: Baseline date was defined as first occurrence of renal biopsy, primary renal diagnosis or symptom presentation. Patients were grouped into those with ESKD (ESKD), or those without ESKD at baseline with a ≥12 months follow-up (CKD group). For survival analyses, ESKD or death was applied with survival time calculated from baseline to last follow-up.

Results: In the ESKD group (n=326), median age at first dialysis (56% of patients) and kidney transplant (7%) was 38 yrs (IQR 29-50). In the CKD group (n=1838), median baseline age was 39 yrs (IQR 28-50) with paediatric onset of disease comprising 6%. Baseline median urine PCR was 1.5 g/g (IQR 0.6-3.2; n=356) and mean eGFR was 58 mL/min/1.73m² (SD 32; n=440). Median follow-up was 9.2 years (IQR 5.1-16.3) and ESKD/death occurred in 53% of patients (~1% death). Kaplan-Meier survival curves of paediatric and adult patients show 50% survival probability of 24 & 10 years, respectively (Figure 1).

Conclusions: RaDaR contains a large cohort with long follow up enabling detailed investigation of the natural history of IgAN. These results indicate associations between rapid disease progression and poor outcomes, highlighting a need for effective treatments for patients with IgAN with renal impairment or >1g/24h proteinuria.

Funding: Commercial Support - Traverse Therapeutics

PO1578

Symptom Burden Among Immunoglobulin A Nephropathy (IgAN) Patients in a US Real-World Setting

Robert M. Perkins,¹ Carolina A. Aldworth,² Raymond Przybylsz,¹ Jim P. Doherty,² Stephen W. Olson,¹ Aneshe T. George,² Jaydeep Das,² Rachel Studer,² Novartis Pharmaceuticals Corporation, East Hanover, NJ; ²Novartis Pharmaceuticals Corporation, East Hanover, NJ; ³Novartis Pharma AG, Basel, Switzerland; ⁴Novartis Healthcare Pvt. Ltd., Hyderabad, India.

Background: Immunoglobulin A nephropathy (IgAN) is the most prevalent chronic glomerulonephritis and 15-40% of patients will progress to end stage kidney disease (ESKD) within 20-20 years of diagnosis. The symptom burden by eGFR and proteinuria levels has not been well described in IgAN and is presented here.

Methods: This is a descriptive, retrospective study of adult (≥18 years) patients in de-identified Optum® Electronic Health Records (2007-2019). Pre-processed physician notes were used to select patients with at least two IgAN records without any secondary or negative notion. Patients without a record of renal biopsy, valid eGFR and proteinuria levels has not been well described in IgAN and is presented here.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

494
levels, or with a history of ESKD/kidney transplant were excluded. The demographic and clinical characteristics, including symptoms up to 12 months before and up to the 1st record of IgAN are presented here; these symptoms were stratified by eGFR and proteinuria levels.

**Results:** The final cohort consisted of 846 patients with a mean age of 48.5 years; 57% were male and 7.0% Asian. Proteinuria levels of ≥ 1 g/day were found in 35.7% of patients. The median eGFR was 39.0 ml/min/1.73m², median creatinine was 1.8 mg/dL, and 20.8% of patients had severe deterioration of kidney function (eGFR <15). Overall, more patients in higher chronic kidney disease (CKD) stages experienced any given symptom but this trend was not consistent for higher proteinuria levels.

**Conclusions:** Our study found that a considerable proportion of patients experienced pain, fatigue and edema. Except in a few instances, all symptoms increased with lower eGFR levels but this trend was less apparent for proteinuria. Our overall findings suggest that a relatively large proportion of IgAN patients, even those with preserved kidney functions could be experiencing substantial symptomatic burden and this warrants further investigation.

**Funding:** Commercial Support - Novartis Pharmaceuticals Corporation

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**PO1579**

**Clinical Outcomes of Kidney Diseases Diagnosed in Active Duty Service Members**

**Trevor W. Tobin,** John S. Thurlow, Robert Nee, Christina M. Yuan. **Walter Reed National Military Medical Center, Bethesda, MD.**

**Background:** There are no studies that have reported glomerulonephritis prevalence and looked at the overall healthcare outcomes following renal biopsies in active duty soldiers. We aimed to determine the prevalence of renal diseases amongst the soldiers biopsied at our institution and determine the outcomes for these individuals as a result of their diagnoses.

**Methods:** In this retrospective study, we evaluated the results of all native renal biopsies performed at Walter Reed National Military Medical Center from 2005 to 2020. We used this data to determine the prevalence of patients who progressed to have ESKD (End Stage Kidney Disease), renal transplantation, creatinine doubling, proteinuria greater than 3.5 g/dL/day, medical evaluation board (MEB), and death. The AHLTA and JLV EMR systems were used to collect data on the patients who met our inclusion criteria. After the data was collected, chi-squared tests were performed and Kaplan-Meier Curves were created for analysis.

**Results:** Among 169 patients (mean age =32 years old; 79% male; 48% white; 37% black; 7% Hispanic; 4% Asian; 3% Pacific islander; 2% other), the most common indication for renal biopsy was for concomitant hematuria and proteinuria (31%) and the most common histologic diagnosis was IgA Nephropathy (23%). The mean time of follow up was 7.3 years. 11% progressed to ESKD, of whom 87% received a kidney transplant (10% overall). Approximately one third progressed to proteinuria greater than 3.5 grams per day and 55% died.

**Conclusions:** We identified IgA Nephropathy as the dominant histologic diagnosis in our patients undergoing renal biopsy between 2005 and 2020. Despite our patients being largely young and healthy individuals, renal biopsy identified severe disease with over 10% of patients progressing to ESKD and 5% mortality.

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**PO1580**

**Clinicopathological Features, Risk Factors, and Outcomes of Immuno- globulin A Nephropathy Associated with Hepatitis B Virus Infection**

**Juchuan Xiong, XinQiao Hospital, Chongqing, China.**

**Background:** Hepatitis B virus (HBV) infections are associated with an increased risk of kidney diseases. However, the effects of HBV infection on the progression of idiopathic A nephropathy (IgAN) are unclear.

**Methods:** A total of 838 patients with biopsy-confirmed IgAN were enrolled in this retrospective cohort study. The patients were categorized into either affected by IgAN and HBV infection (HBsAg-IgAN) or by primary IgAN with no sign of HBV infection (P-IgAN). A 1:1 propensity-score matching was performed between the two groups, followed by a Kaplan-Meier survival analysis, to compare the prognoses, and a Cox regression analysis, to identify factors influencing the HBsAg-IgAN outcomes.

**Results:** A total of 176 pairs of patients were successfully matched. A significant difference in the systolic blood pressure and urea, serum creatinine, uric acid, and 24-h urine protein levels was observed between the groups. A renal pathological analysis also revealed a significant difference in the mesangial hypercellularity between the groups. During a median follow-up period of 2.4 years, Kaplan-Meier analysis also revealed a significant difference in the renal survival between the groups. Furthermore, multivariate Cox analysis confirmed that HBV infection is an independent risk factor for IgAN progression (hazard ratio [HR] 2.996; 95% confidence interval [CI] 1.091–4.026). Finally, the HBsAg-IgAN patients who received treatment with renin-angiotensin-aldosterone system inhibitors had a better overall prognosis than those who received immunosuppressive therapy and antiviral treatment.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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**PO1581**

**Factors Associated with ESKD in Mexican Patients with IgA Nephropathy: A Single-Centre Retrospective Cohort Study**

**Daniela Xavier,** Guadalupe Ramos De Jesus, Octavio R. Garcia-Flores, Bernardo Moguel. **Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.**

**Background:** IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world among patients undergoing renal biopsy. To standardize the histological findings, the Oxford Classification (OC) has allowed clarifying kidney lesions that confer potential risk of progression. The aims are describe the factors associated with ESKD and treatment implemented in Mexican patients with IgAN.

**Methods:** We conducted a single-center, retrospective cohort study in a tertiary hospital in Mexico City, patients with biopsy-proven IgAN and followed up for at least 2 years and examined the relationship between clinical parameters and OC to predict the risk of ESKD after biopsy. We used age and sex adjusted Cox proportional hazards models to study the association of the predictor variables (MEST-C, global glomerulosclerosis and proteinuria >1 g/day) with the incidence of ESKD. The HRs were expressed with 95% confidence intervals (95% CI).

**Results:** 35 patients were included, mean age 37.2±15.2 years, 60% were female, mean eGFR and proteinuria at biopsy were 60.8±34.6 ml/min/1.73m² and 3.4±4.0 g/dL/day respectively. ESKD or eGFR decline by ≥50% as compared to baseline occurred in 10 patients (28.6%) in of follow-up of 2 years. The eGFR at 24 months post-biopsy 39.1±39.6 ml/min/1.73m². 18 patients received immunosuppressive treatment and 24 received prednisone. The distribution of MEST-C lesions were: M1=35(100%), E1=20(57.1%), S1=33(94.3%), T1=15(42.9%) and T2=7(20.6%), C1=11(31.4%) and podocytopathic features in 3(8.5%). Of the MEST-C components, only T2 was significantly associated with ESKD (HR 4.66, 95% CI 0.8 to 27.1). After adjusting for confounding variables global glomerulosclerosis >50% (HR 1.92 [1.02-3.58], p=0.001) and New oxford classification system (O-grade) grade III (HR 2.79 [0.89-8.58], p=0.001) were independently associated with ESKD.

**Conclusions:** There are no reports in Mexico of clinical characteristics and outcomes of IgA nephropathy. This study demonstrates that IgA nephropathy was more common in young adults and women and that the progression to ESKD or the global glomerulosclerosis >50% is similar to the reported in the literature. IFTA >50%, and O-grade III were associated with the development of ESKD in Mexican population.

**PO1582**

**External Validation of Two New IgA Risk-Prediction Tools in a Norwegian Cohort**

**Nynvar Lunde Haaska,1 Njalur Lura,1 Rune Bjorneklett,1,2 Lars S. Bostad,1,2 Thomas Knop,1,2 Haukeland Universitetssjukehus, Bergen, Norway; 1Universitetet i Bergen, Bergen, Norway.**

**Background:** Recently two prediction tools for IgA nephropathy (IgAN) have been developed combining clinical and histopathological parameters. Barbour and colleagues developed the International IgAN Prediction Tool, to predict the risk for 50% decline in estimated glomerular filtration rate (eGFR) or end stage renal disease (ESRD) up to 80 months after diagnosis. Schena and colleagues developed the IgA Nephropathy Clinical Decision Support System (CDSS), using artificial neural networks (ANN) to estimate the risk for ESRD. In the present study we aim to externally validate both prediction tools using a Norwegian cohort with long-term follow-up.
POI1583

International IgA Nephropathy Network (IIgANN) Risk Prediction and Longitudinal Outcomes in the First South-Asian Prospective IgA Nephropathy Cohort (GRACE-IgANI)

Suceena Alexander,1 Santosh Varughese,1 Atlul Thomas,1 Jeethu J. Eappen,1 Elenjickal E. John,1 Anna T. Valson,1 Vinici G. David,1 Mohamed R. Daha,2 George John,1,3 John Fechely,3 Jonathan Barratt,4 Christian Medical College Vellore, Vellore, India; 2Universitair Medisch Centrum Groningen, Groningen, Netherlands; 3Royal Brisbane and Women’s Hospital, Herston, QLD, Australia; 4University of Leicester College of Life Sciences, Leicester, United Kingdom; 5University of Leicester, Leicester, United Kingdom.

Background: The Glomerular Research And Clinical Experiments- IgA Nephropathy in Indians is a prospective longitudinal cohort registered with WHO trial id: ISRCTN36834159. The performance of the IIgANN risk prediction score (Barbour et al.) has not been assessed in South Asian IgAN.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 195 patients (97%) completed 3 year longitudinal follow-up. Of these, 180 patients had complete Oxford MEST-C score at baseline. Composite outcome (CO) was defined as ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m2 or RRT/death.

Results: The median predicted 3-year risk of a ≥50% decline in eGFR or ESKD using the IIgANN risk prediction tool was 18.1% (IQR 7.4–31.2) at baseline. The minimum score was 0.64% and the maximum was 55%. Short course IS was used in 146/201 (73%) of patients. 72 patients (36.9%) experienced CO over 3 years. The median risk in patients with favourable outcome was 13.15% (IQR 4.2–21.7) and in those with CO was 32.2% of patients. 72 patients (36.9%) experienced CO over 3 years. The median risk in patients the IIGANN risk prediction tool was 18.1% (IQR 7.4–31.2) at baseline. The minimum RRT/death.

180 patients had complete Oxford MEST-C score at baseline. Composite outcome (CO) kidney biopsy. 195 patients (97%) completed 3 year longitudinal follow-up. Of these, has not been assessed in South Asian IgAN.

Conclusions: Both prediction tools perform well and could become helpful tools for clinicians to identify patients at risk. Barbour’s tool seems to lose prognostic discriminative value at a faster rate than Schena’s over time.

POI1584

IgA Nephropathy Histopathology and Long-Term Renal Prognosis

Nora C. Maddy, Robert Nee, Sarah M. Gordon, Stephen W. Olson. Walter Reed National Military Medical Center, Bethesda, MD.

Background: The Oxford Classification established the mesangial hypercellularity (M), Endocapillary hypercellularity (E), segmental sclerosis (S), Tubulointerstitial fibrosis (T), and crescents (C) score as an important prognostic tool for IgA nephropathy (IgAN). However, these studies did not investigate the impact of complement 3 (C3) immunofluorescence (IF) staining or interstitial inflammation (iI) on long term renal outcomes, nor evaluate an ethnically diverse population which included African Americans.

Methods: We queried the military health system (MHS) by ICD-9/10 codes to identify potential IgA nephropathy cases. We then reviewed the electronic medical record to find those with biopsy-proven IgA nephropathy. Prespecified clinical data was collected to include MEST-C scores, iI, and C3 IF. Primary outcomes included >50% decline in estimated glomerular filtration rates (eGFR), chronic kidney disease (CKD) with eGFR <60ml/min/1.73m2, and end-stage kidney disease (ESKD).

Results: 172 patients were identified with a mean follow-up of 11 years. Mean age was 32 years; 77.9% male; 64.5% White, 9.9% Black, and 12.2% Asian/Pacific Islanders. C3 IF≥2+ was significantly associated with ESKD (p=0.03) and >50% decline in eGFR (p=0.02). If ≥15% was significant for ESKD (p=0.003), CKD (p=0.01), and >50% decline in GFR (p=0.01). T and C scores were significant for ESKD, CKD, and >50% decline in GFR (all p<0.001). S score was significant for ESKD (p=0.02) and CKD (p=0.009). E score was significant for CKD (p=0.003). M score was not significant for any of the primary outcomes.

Conclusions: We present histopathology associated long term renal outcome data for the most ethnically diverse IgAN cohort with the longest follow up to date in such a population. Our data suggests that degree of C3 staining on IF and amount of interstitial inflammation could augment the prognostic accuracy of the MEST-C score. In addition, it supports the theory that IgA immune complexes activate the alternative complement pathway which drives significant interstitial inflammation ultimately resulting in tubular atrophy and interstitial fibrosis. Disclaimer: The views expressed are those of the authors and do not reflect official policy of the Department of the Army/Navy/Air Force, Department of Defense, or United States government.
PO1585
Severity of Arterial and Arteriolar Sclerosis in IgA Nephropathy and Effects of Renin-Angiotensin System Inhibitors on Its Prognosis
Naoko Sugiuara, Takahito Moriyama, Yoci Miyabe, Kenichi Akiyama, Kazunori Karasawa, Kosaku Nitta. Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.

Background: IgA nephropathy (IgAN) patients often suffer from renal arterial intimal thickening (AIT) and arteriolar hyaline (AH) however, it is unclear whether these features are associated with a poor prognosis. This study aimed to analyze whether treatment with renin-angiotensin system inhibitors (RASI) improves those patient’s survival.

Methods: This retrospective cohort analysis included total 871 patients with IgAN, grouped according to the absence or presence of AIT (Study 1; AIT0: n=415, AIT1: n=268) or AH (Study 2; AH0: n=405, AH1: n=354). The clinical, laboratory, and histological backgrounds of the patients were analyzed along with their 20-year renal prognosis. In the AIT1 and AH1 groups, the effect of renin-angiotensin system inhibitors (RASI) on renal prognosis after making adjustments for the background was analyzed and risk factors for progression were also analyzed.

Results: IgAN patients with AIT1 or AH1 had significantly higher age, blood pressure, body mass index, total cholesterol, uric acid levels, and proteinuria than patients with AIT0 or AH0. They also had more marked histologic findings, decreased renal function, and lower survival rates (AIT: 62.2% vs. 83.4%, P=0.0001; AH: 63.5% vs. 85.4%, P=0.0001). Multivariate Cox regression analysis considering with clinical and histological findings and treatments revealed AIT and AH as an independent factor for disease progression (AIT1: hazard ratio [HR], 1.98, 95% confidence interval [CI], 1.01-3.97; AH1: HR, 2.12, P=0.014). The renal survival rate was significantly higher in IgAN patients with AIT0 or AH0 who were treated with RASI than in those who were not treated with RASI after background adjustments (AIT: 71.1% vs. 50.4%, P=0.023; AH: 76.4% vs. 39.5%, P=0.006). RASI was found to be an independent factor in the prevention of progression, by multivariate Cox regression analysis (AIT1: HR, 0.40, 95% CI, 0.14-1.16; AH1, 0.42, P=0.07).

Conclusions: AIT and AH are associated with serious clinical, laboratory and histological findings and a poor prognosis. RASI was found to improve renal prognosis of those patients.

PO1586
Intensity of Glomerular Galactose-Deficient IgA1 Deposition Can Be a Marker of Disease Activity in IgA Nephropathy
Maiko Nakayama,1 Hitoshi Suzuki,2 Yusuke Fukao,3 Mingfeng Lee,1 Toshiki Makita,1 Yuyuko Matsumoto,1 1Department of Nephrology, Juntendo University Nerima Hospital, Tokyo, Japan; 2Department of Nephrology, Juntendo University Urayasu Hospital, Chiba, Japan; 3Department of Nephrology, Juntendo University Nerima Hospital, Tokyo, Japan.

Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the development of IgA nephropathy (IgAN). Recently, it was reported that Gd-IgA1 specifically deposit on glomeruli of primary IgAN using Gd-IgA1-specific monoclonal antibody (KM55 mAb). However, the association between the intensity of Gd-IgA1 deposition and clinical course and histological severity is not clarified.

Methods: We performed immunostaining with KM55 mAb on paraffin sections of IgAN tissues. We divided patients into tertiles according to the amount of Gd-IgA1 deposition intensity of glomerular Gd-IgA1 by Image-J software, and analyzed its association with specific histological findings and treatments revealed AIT and AH as an independent factor for disease progression. In the AIT1 and AH1 groups, the effect of renin-angiotensin system inhibitors (RASI) on renal prognosis after making adjustments for the background was analyzed and risk factors for progression were also analyzed.

Results: Patients with M1, E1, S1, and C1 scores according to the Oxford classification (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental sclerosis; T, tubular atrophy/intertubular fibrosis; and C, crescents) were examined using Kaplan-Meier analysis and Cox regression analysis. The steroid responder score (SRS) and steroid non-responder score (SNRS) were determined using the obtained results. The effects of steroid therapy on renal prognosis according to the combination of the total SRS and SNRS for IgAN were analyzed using Cox regression analysis.

Conclusions: Steroid therapy improved the 20-year renal survival rates in all IgAN patients (steroid (+): 75.5% vs. steroid (-): 61.7%, P=0.025) and patients with M1, E1, S1, C1, and T0 scores. We recognized the total score of M1, E1, S1, and C1 scores (0–4 points) as the SRS and that of T1 and T2 scores (0–2 points) as the SNRS. Multivariate Cox regression analysis revealed that steroid therapy improved the long-term renal prognosis in IgAN patients with higher SRS and lower SNRS (SRS4/SNRS0: hazard ratio [HR], 0.08 and P=0.008; SRS3/SNRS5: HR, 0.05 and P=0.025; SRS4/SNRS1: HR, 0.11 and P=0.007), but not in IgAN patients with lower SRS (0–3) SNRS1 and any SRS/SNRS2.

PO1587
Segmental Necrotizing/Crescentic Glomerulonephritis (SGN) in IgA Nephropathy (IgAN): A Single-Center Experience
Niral B. Ramani, William L. Whittier, Stephen M. Korbet. Rush University Medical Center, Chicago, IL.

Background: The presence of SNGN on renal biopsy generally portends a poor prognosis, and is typically treated with immunosuppressive agents. The association of pts with IgAN to determine if the presence of SNGN portends a poorer prognosis in this pt population.

Methods: Biopsies done at Rush University Medical Center from 1992-2019, found SNGN in 35 pts (21 males). Of these 35 pts, 1 of which had M0 (0%) and 24 of which had M1 (69%) SNGN was seen in 21 (60%). Clinical, laboratory, histologic features at biopsy, treatment and outcome data (doubled of SCr and ESKD) were collected retrospectively. Pts with and without SNGN were compared. Data is presented a meansSD and a P value of <0.05 was significant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

PO1588
Novel Scoring System Based on the Oxford Classification Indicating Steroid Therapy Use for IgA Nephropathy
Takahito Moriyama, Eri Kasama, Yoci Miyabe, Kenichi Akiyama, Kazunori Karasawa, Kosaku Nitta. Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.

Background: The Oxford classification identifies predictors of the renal prognosis for IgA nephropathy (IgAN); however, it has been unclear about usefulness for deciding the management approach. We analyzed the clinical utility of this classification for indicating steroid therapy.

Methods: The effects of steroid therapy on the long-term prognosis for all 858 IgAN patients and patients divided with M0, M1, E1, S1, T0, T1, T2, C1, and C2 scores according to the Oxford classification (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental sclerosis; T, tubular atrophy/intertubular fibrosis; and C, crescents) were examined using Kaplan-Meier analysis and Cox regression analysis. The steroid responder score (SRS) and steroid non-responder score (SNRS) were determined using the obtained results. The effects of steroid therapy on renal prognosis according to the combination of the total SRS and SNRS for IgAN were analyzed using Cox regression analysis.

Results: Steroid therapy improved the 20-year renal survival rates in all IgAN patients (steroid (+): 75.5% vs. steroid (-): 61.7%, P=0.025) and patients with M1, E1, S1, C1, and T0 scores. We recognized the total score of M1, E1, S1, and C1 scores (0–4 points) as the SRS and that of T1 and T2 scores (0–2 points) as the SNRS. Multivariate Cox regression analysis revealed that steroid therapy improved the long-term renal prognosis in IgAN patients with higher SRS and lower SNRS (SRS4/SNRS0: hazard ratio [HR], 0.08 and P=0.008; SRS3/SNRS5: HR, 0.05 and P=0.025; SRS4/SNRS1: HR, 0.11 and P=0.007), but not in IgAN patients with lower SRS (0–3) SNRS1 and any SRS/SNRS2.

Conclusions: Patients who responded to steroid treatment; contrarily, those with T1 and T2 scores did not. A higher SRS was a useful indicator for steroid therapy. Nevertheless, prevention of progression in IgAN patients with SRSN was difficult with steroid therapy.
Remission of Hematuria Is Associated with Favorable Prognosis in IgA Nephropathy

Kyung Ho Lee, Young seung Oh, Moo Yong Park, Soo Jeong Choi, Jin kuk Kim, Seung D. Hwang, Byung chul Yu. Soonchunhyang University Hospital Bucheon, Bucheon, Gyeonggi-do, Republic of Korea.

Background: Recent studies have shown that remission of hematuria is associated with favorable clinical outcomes in patients with immunoglobulin A nephropathy (IgAN). The current study was conducted to compare the long-term clinical outcomes between patients with remission of hematuria and those with persistent hematuria using the stricter but intuitive definition of “remission of hematuria” than that used in previous studies.

Methods: This retrospective, multicenter, observational study was conducted using a cohort of patients diagnosed with IgAN through kidney biopsy at three tertiary hospitals. A total of 403 patients who had been followed up for more than 3 years and who underwent regular check-ups at intervals of at least 6 months were enrolled. Hematuria remission was defined as the presence of hematuria for at least 3 months after biopsy for diagnosis but with no RBC per high-power field observed in the urine under the microscope for at least 2 years thereafter.

Results: The mean annual rate of eGFR decline was lower in the remission of hematuria group than in the persistent hematuria group (-1.51 ± 2.86 vs. -2.60 ± 3.18 mL/min/1.73 m²/year, p = 0.002). In the remission of hematuria group, the mean annual rate of eGFR decline decreased after hematuria disappearance (from -1.28 ± 7.06 to 0.09 ± 0.29 mL/min/1.73 m²/year, p = 0.016). Multivariable analysis revealed remission of hematuria as an independent predictor of a 50% reduction in kidney function (hazard ratio, 0.55; 95% CI, 0.33 to 0.99). Renal survival, defined as a 50% reduction in kidney function, was better in the remission of hematuria group than in the persistent hematuria group (p = 0.030). However, free of ESRD was not significantly different between the two groups (p = 0.079).

Conclusions: In this study, which used a more rigorous but intuitive definition of hematuria remission than that used in previous studies, patients with remission of hematuria showed favorable kidney prognosis. This new definition for remission of hematuria could be used as a prognostic marker in actual clinical practice.

Comparison of renal outcomes between the two groups

Reduction of Urinary Levels of Lectin Pathway Complement Components in an IgA Vasculitis Patient After MASP-2 Inhibition with Narsoplimab

Laura Pérez Alós, Katrin Sciorti, Karen Molyneux, Jonathan Barratt, Peter Gurr. Rigshospitalet, Copenhagen, Denmark; 2 University of Leicester, Leicester, United Kingdom; 3 Leicester General Hospital, Leicester; United Kingdom.

Background: A young female suffering from IgA vasculitis was treated with 4 mg/kg weekly infusions of narsoplimab (a MASP-2 inhibitor) for 12 weeks. MASP-2 is considered the key activator of the lectin pathway (LP) by cleaving C4 and C2, after the binding of LP pattern recognition molecules to its ligands. Inhibition of MASP-2 is predicted to decrease complement activation in complement-mediated kidney diseases. In this exploratory study, we measured the levels of different LP complement components to evaluate the influence of narsoplimab on complement activation.

Methods: Urine levels of complement activation markers (C4c, C3bc and soluble C5b-9) and urine levels of ficolin-1, 2 and 3, MBL, CL-11, MASP-3, MASP-1 and PTX-3 were measured using sandwich-ELISAs. Urine samples were subjected to LC/MS-MS. Correlations between LC/MS-MS and sandwich-ELISAs were conducted using simple linear regression and Spearman's rank correlation coefficient. Significance: p value < 0.05. Urine proteins were adjusted for creatinine excretion and expressed as specific protein/creatinine ratio.

Results: C4c:creatinine ratio, ficolin-3:creatinine ratio and C3bc/creatinine ratio levels were decreased 75%, 58% and 29%, respectively, from baseline to the end of the treatment; while levels of MBL and CL-11 remained stable during the treatment. C4c/creatinine ratio levels were significantly correlated to LC/MS-MS C4 data (R²: 0.5059; Spearman: r = 0.5824, p = 0.0402). Circulating levels of complement components in serum were unaltered during treatment. Soluble C5b-9, ficolin-1, -2, MASP-3 and MASP-1 were undetectable in urine and PTX-3 was undetectable in both urine and serum.

Conclusions: This is the first report describing the effect of narsoplimab on urinary complement levels in a complement-mediated kidney disease. Our data suggest a decrease in local complement activation with narsoplimab treatment. Further studies are ongoing to evaluate the use of urine as a non-invasive, inexpensive and readily accessible resource to monitor responses to complement-directed treatments.

Funding: Commercial Support - Omeros Corporation
GWAS methods. The results were tested for Hardy-Weinberg equilibrium (control group; 136-unmatched healthy controls (mean age 48.7
±2.9 patients (mean age 42.9
±2.2Department of Clinical Immunology, Medical University of Warsaw, Warsaw, Michał Pac,1 Natalia Krata,1 Beata Kaléta,2 Barbara Moszczyk,1,2 Aleksandra Wyczalkowska-Tomasik,1 Julia Prystupa,1 Krzysztof Krylik,1 Krzysztof Mucha,1,4 Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; Department of Clinical Immunology, Medical University of Warsaw, Warsaw, Poland; Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, NY; Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland.

Background: In other diseases (ex. asthma and pemphigus vulgaris) NR3C1 single nucleotide polymorphisms (SNPs) were associated with glucocorticoid (GC) treatment outcomes. The aim of the study was evaluation of the frequency of NR3C1 (SNPs) in adult membranous (MN) and IgA (IgAN) nephropathies biopsy proven patients.

Methods: We used two approaches to establish a transcriptional signature of ET-activation. First, using a targeted approach, an ET-activation network was generated using three publicly available datasets, produced a gene list of 60 transcripts to create an activity score which was assessed in kidney biopsy profiles in patients with IgAN (n = 25) from the European Renal DNA Bank (ERCB). In addition, an ET-activation signature was also generated using RNAseq profiling of human MCs isolated with ET1 (4nM) /- the selective ET receptor antagonist (1nM, 25nM, n=3/group). Pairwise differential gene expression and gene set enrichment analysis (GSEA) was performed.

Results: The targeted analysis showed that the ET-activity score correlated with increased proteinuria (r=0.42, p=0.05) and decreased eGFR (r=0.47, p=0.02) in patients with IgAN. The transcript network showed enrichment in endothelial and mesangial cell clusters in renal single cell RNASeq profiles. Differential expression analysis identified the ET gene network was reversed by atorvastatin in MCs (25nM, n=7–8 genes, q<0.05). GSEA in MCs revealed up-regulation of cell proliferation, inflammatory and fibrotic clusters, with ET1 treatment, which were blocked by atorvastatin.

Conclusions: We generated an ET-activation score using a systems biology approach to identify patients with IgAN. ET-receptor antagonists were associated with progression, providing additional support for the therapeutic potential of ETA receptor blockade in IgAN patients at high risk of progression. Ongoing work is focused on optimizing the signature, extending findings to additional cohorts and identifying mechanistic biomarkers.

Funding: Other NHI Support - Federal grant, Commercial Support - Chinnok Therapeutics

PO1594
NR3C1 Polymorphisms in Membranous and IgA Nephropathies
Michał Pac,1 Natalia Krata,1 Beata Kaléta,2 Barbara Moszczyk,1,2 Aleksandra Wyczalkowska-Tomasik,1 Julia Prystupa,1 Krzysztof Krylik,1 Krzysztof Mucha,1,4 Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; Department of Clinical Immunology, Medical University of Warsaw, Warsaw, Poland; Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, NY; Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland.

Background: In other diseases (ex. asthma and pemphigus vulgaris) NR3C1 single nucleotide polymorphisms (SNPs) were associated with glucocorticoid (GC) treatment outcomes. The aim of the study was evaluation of the frequency of NR3C1 (SNPs) in adult membranous (MN) and IgA (IgAN) nephropathies biopsy proven patients.

Methods: We analyzed SNPs: rs6198, rs14123247 and rs17209237 in 39 MN patients (mean age 42.9±14.2, y; 34 ½, 39 sex- and age-matched and 35-unmatched IgAN patients (mean age 33.5±12.3, y; 34 ½ and 39 sex- and age-matched and 136-unmatched healthy controls (mean age 48.7±17.9, y; 89 ½) using RT-PCR and GWAS methods. The results were tested for Hardy-Weinberg equilibrium (control group; p<0.05) and compared between MN, IgAN and controls and within MN and IgAN between GC-resistant and -sensitive and GC-dependent and -independent groups using the γ2 with Yates’s correction test.

Results: The frequency of the minor C allele of rs6198 SNP was significantly increased in MN (p=0.05) and IgAN (p=0.05) compared to controls; and in GC-resistant MN (p=0.05), GC-resistant (p=0.05) and GC-dependent (p=0.05) IgAN. The rs6198 SNP genotypes were unequally distributed among GC-resistant patients (p=0.05) and GC-dependent (p=0.05) IgAN. The frequency of the major A allele of rs17209237 was significantly increased in GC-sensitive (p=0.05) and -independent (p=0.05) IgAN. There was a disequilibrium in rs17209237 SNP distribution among GC-sensitive and GC-resistant patients (p=0.05). The minor C allele was significantly more frequent among MN (p=0.05) and IgAN (p=0.05) relapse patients and there was rs6198 genotypes distribution inequality for these both groups (p<0.05).

Conclusions: Rs6198 and rs17209237 alleles and genotypes have different distribution between MN and IgAN and -GCs and controls; and between patients differently responding to the GC treatment. Results indicate that they predict GC treatment outcomes and therefore should be further investigated for their potential prognostic value.

PO1595
A Rare Case of Paraneoplastic IgA Nephropathy in the Setting of Renal Cell Carcinoma
Alka A. Tyagi, Mohankumar Doraswimy, Sethu M. Madhavan. The Ohio State University Wexner Medical Center, Columbus, OH.

Introduction: Paraneoplastic nephropathy can present in patients with malignancy. Renal cell carcinoma (RCC) is the most common urologic malignancy; there is a paucity of reported paraneoplastic nephropathies associated with this condition. As such, we present an intriguingly unique case of nephrotic range proteinuria in the setting of recurrent, metastatic renal cell carcinoma.

Case Description: An 81-year-old male with history of recurrent metastatic RCC, solitary kidney after a nephrectomy, with stage III chronic kidney disease (CKD) presents with newly worsening renal function. In a 3-month span, his creatinine (C) rose from 3.5 mg/dL to 4.6 mg/dL, which prompted further workup. He had a history of prostate cancer and his most recent biopsy showed adenocarcinoma. His chart was notable for recurrent, metastatic renal cell carcinoma.

Discussion: Acutely worsening renal function and nephrotic range proteinuria in the setting of malignancy prompts investigation into a paraneoplastic nephropathy. As in this case, secondary IgA mesangial nephropathy can rarely present with RCC. This association is rare and furthermore there is a lack of understanding of the development of this glomerulopathy. Treatment of the underlying malignancy has shown to improve and preserve renal function. Further investigation into the immune-pathophysiology can help drive the development of further treatment strategies.

PO1596
Circulating and Depositing Glomerular Antibodies: A Concurrence or Coexistence
Deepti Avanavelli, Dhanalakshmi Vurum, ESIC Medical College and Hospital Hyderabad, Hyderabad, India.

Introduction: Anti-GBM disease is a systemic autoimmune disorder characterized by circulating IgG antibodies (rarely IgA and IgM), may coexist with pauci-immune crescentic/necrotizing/cyclosporin-responsive chronic interstitial nephritis, and membranous glomerulopathy. The concurrent or sequential presentation of anti-GBM disease with IgA nephropathy has been rarely described.

Case Description: We herein report a case of 51-year-old female who had presented with sudden onset of breathlessness, pedal oedema for 15 days and oliguria for 5 days with 1 episode of haematuria. There were no arthralgias, oral ulcers, alopecia, skin rash, sore throat and diarrhoea. Her marital life was of five years with no history of conception and pregnancy. She had undergone tonsillectomy for chronic tonsillitis and adenoids. Her medical history was otherwise unremarkable. She had a past history of hypertension for 4 years and recently undergone a nephrectomy for stage III chronic kidney disease (CKD) presented.

Discussion: In the setting of malignancy, paraneoplastic nephropathy has been rarely described. The concurrent or sequential presentation of anti-GBM disease with IgA nephropathy has been rarely described.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: Presentation of IgAN along with anti GBM without linear deposition on renal biopsy but with positive anti GBM titers makes this case interesting. The association of anti GBM disease with IgAN nephropathy could be a coexistence as IgAN is most common glomerular disease or these IgA mesangial deposits might have role in the pathogenesis of triggering GBM antigens and formation of antibodies in this case.

POI1597
Early Predictors of Stable Kidney Function in Lupus Nephritis
Juan M. Mejia-Vilet, Megan Ashley N. Gerrard, Roque A. Comunidad Bonilla, Luis E. Morales-Buenrostro. National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico.

Background: Early prediction of outcomes in LN is essential to adjust LN treatment. The aim of this study was to evaluate the early course of laboratory parameters and their association with long-term stability of kidney function.

Methods: We studied 433 patients from our local LN cohort recruited between 2008 and 2017. All patients had >36 months follow-up and complete evaluation at LN flare, 3-, 6-, and 12-months of follow up with hemoglobin, creatinine, 24h-proteinuria, albumin, anti-dsDNA-Ab, complement C3 and C4 fragments. The main outcome was stable kidney function defined as eGFR within 25% of the best eGFR attained in the first 12 months of treatment. Each variable was evaluated individually by ROC curves and in association with other variables. The change in area under the curve (AUC) was analyzed with De Long's test.

Results: Median follow up was 73 months (IQR 51-101). Kidney survival was 90% and 81% at 3- and 5-years, respectively. Stability of kidney function was 77% and 65% at 3- and 5-years, respectively. The predictive performance of each parameter varied with the timepoint where evaluated (Table). Serum albumin and hemoglobin AUCs improved from baseline to the 3- and 6-month timepoint. Proteinuria and eGFR AUCs improved at each timepoint up to the 12-month timepoint. C3, C4, and anti-dsDNA-Ab level did not improve at any timepoint vs. baseline. The best predictor of 36-month eGFR stability was proteinuria <1g/d by 12 months. The sum of proteinuria plus eGFR provided the best combined AUC at each timepoint (Figure 1).

Conclusions: Early course of albumin, hemoglobin, and serological parameters does not improve prediction for stable kidney function in LN. The predictive performance of each biomarker improves over time. The combination of proteinuria and eGFR remains the best predictor of kidney outcomes.

Table 1. Area under the curve (AUC) of the evaluated parameters to predict stable kidney function by 36 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>0.72 (0.68-0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.54 (0.49-0.59)</td>
<td>0.023</td>
</tr>
<tr>
<td>Proteinuria + eGFR</td>
<td>0.75 (0.71-0.79)</td>
<td>&lt;0.001</td>
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Figure 1. ROC curves of proteinuria (A), eGFR (B), and the sum of proteinuria plus eGFR (C) to predict stable kidney function by 36 months.

POI1598
Long-Term Outcomes of Lupus Nephritis in a Single Tertiary Care Center in South India
SriniVasa N. Kinjarapu, Swamalatha Geduti, Siddharth Herur. Nizam’s Institute of Medical Sciences, Hyderabad, India.

Background: Lupus nephritis (LN) is a frequent and severe manifestation of SLE. It is a risk factor for chronic kidney injury and end-stage renal disease in SLE we evaluated the clinical presentation and outcome with various treatment regimens in patients with lupus nephritis.

Methods: A retrospective study in 50 patients with biopsy proven LN [class III (12), class IV (11), class V (4), class III+IV (10), class III+V (7), class IV+V (6)] treated with NMP for 3 days followed by monthly CYC for 6 months and oral corticosteroids 0.5-1mg/kg with tapering to 10mg/day at the end of 6th month as induction protocol. AZA or MMF as maintenance regimen based on clinician discretion. Clinical presentation, histopathological (LM+IF) features, treatment regimen, treatment response and renal relapse and outcome were evaluated.

Results: Patients had a mean follow up of 3.6 years, clinical presentation nephrotic syndrome were seen in 42 (84%) patients. Most frequent IGs were present in 29 (58%) patients, of which 24 (48%) patients were female (87.5%) and black (87.5%). Mean serum creatinine (Sr Cr) was 3.1mg/dL and proteinuria by 24-hour urine collection or spot urine protein:creatinine ratio was 7.12g. Excluding 2 patients with limited follow-up, 11 of 14 (78.6%) patients had poor renal outcomes. These patients were similar in age (mean 33 years) and were also majority female (90.1%) and black (90.1%). In this group, mean Sr Cr was 5.35mg/dL and proteinuria was 3.69g. This group had significant interstitial fibrosis and tubular atrophy compared to patients with 71% moderate and 28% severe IFTA. Therefore the requirement for renal replacement therapy at end of 5 years (average). Of 3 patients who did not have a renal end point, mean Sr Cr was 1.83 mg/dL with less IFTA noted on biopsy. Treatment options varied with most receiving mycophenolate or cyclophosphamide.

Conclusions: This descriptive project confirmed that CG was associated with poor renal prognosis in LN; the majority of the patients required dialysis, proceeded to transplantation, or had doubling of serum creatinine during follow up. Despite treatment with standard of care agents, outcomes remained poor. Patients who had worse Sr Cr at presentation or severe IFTA had worse outcomes.

POI1600
Collapsing Glomerulopathy Can Worsen Prognosis in Lupus Nephritis

Background: Collapsing glomerulopathy (CG) conveys a poor renal prognosis and is characterized by podocytopathy with segmental or global collapse of the capillary walls. While it can be idiopathic, it is often seen in association with other viral, drug, and autoimmune conditions including lupus nephritis (LN). This retrospective study describes features and clinical outcomes of 16 patients with SLE and biopsy proven CG.

Methods: Using our Glomerular Disease Collaborative Network registry, we performed retrospective chart review on patients with systemic lupus erythematosus and CG on kidney biopsy with or without an LN lesion from 2000 - 2021. Patients with multiple biopsies, the first biopsy with GC was identified as the incident biopsy. We defined poor renal outcome as reaching a renal endpoint of serum creatinine doubling, chronic dialysis initiation, or renal transplantation. Patients were characterized by baseline demographics, laboratory results, CG on kidney biopsy with or without LN lesion, treatment received, and the number and type of previous appointments (dichotomized into ≤5 vs. >5).

Results: We identified 16 patients with mean age of 33 years at incident biopsy. Most were female (87.5%) and black (87.5%). Mean serum creatinine (Sr Cr) was 3.1mg/dL and mean proteinuria by 24-hour urine collection or spot urine protein:creatinine ratio was 7.12g. Excluding 2 patients with limited follow-up, 11 of 14 (78.6%) patients had poor renal outcomes. These patients were similar in age (mean 33 years) and were also majority female (90.1%) and black (90.1%). In this group, mean Sr Cr was 5.35mg/dL and proteinuria was 3.69g. This group had significant interstitial fibrosis and tubular atrophy compared to patients with 71% moderate and 28% severe IFTA. Therefore the requirement for renal replacement therapy at end of 5 years (average). Of 3 patients who did not have a renal end point, mean Sr Cr was 1.83 mg/dL with less IFTA noted on biopsy. Treatment options varied with most receiving mycophenolate or cyclophosphamide.

Conclusions: This descriptive project confirmed that CG was associated with poor renal prognosis in LN; the majority of the patients required dialysis, proceeded to transplantation, or had doubling of serum creatinine during follow up. Despite treatment with standard of care agents, outcomes remained poor. Patients who had worse Sr Cr at presentation or severe IFTA had worse outcomes.
PO1601

Serological Activity in Pure Membranous Lupus Nephritis in a Predominantly Black Population
Levard G. Roberts, Aakriti Arora, Hilton Mozee, Jason Cobb. Emory University, Atlanta, GA.

Background: Clinically significant kidney disease is estimated to occur in nearly 60% of patients with systemic lupus erythematosus (SLE). A majority of these patients develop proliferative disease, however 10-15% develop a non-proliferative form of disease known as membranous lupus nephritis (LN) (Class V lupus nephritis). These patients typically present with significant proteinuria. Austin et al. reported 7% of patients with low complements levels and 21% with elevated anti-dsDNA levels. In this study we assess serological activity (C3, C4, anti-dsDNA) of pure membranous LN in a predominantly black patient population.

Methods: Kidney biopsy log from 2010 – 2017, and a retrospective chart review was completed. We excluded any patients with proliferative disease (active or chronic). We analyzed serological activity (C3 level, C4 level & anti-dsDNA) at time of renal biopsy and again at 24 weeks.

Results: Of the total 101 patients with pure membranous LN, we had 54 patients with sufficient follow-up data. 52 of the 54 patients were female with an average age of 35.5; 92.5% (50 of 54) were black. At time of kidney biopsy, low C3 and low C4 was found in 54% and 41% of patients respectively. Whereas an elevated anti-dsDNA was identified in 39% with 20% having the classic triad of low C3, low C4 and elevated anti-dsDNA. When compared to 24 weeks (roughly end of induction therapy) low C3 and low C4 was found in 37% and 24% of patients respectively. Whereas an elevated anti-dsDNA was identified in 31% with 13% have the combination of low C3, low C4 and elevated anti-dsDNA.

Conclusions: In this predominantly black population of pure membranous LN the majority of patients did not have the classic triad of low complements and elevated dsDNA (20% at time of diagnosis/biopsy). Compared to others looking at pure membranous we did find higher rates of low complements and elevated anti-dsDNA at time of diagnosis (54% with low C3 initially). Possibly due to our unique urban patient population which is >90 percent black, i.e. more severe SLE. Despite the majority of patients not having the classic triad of low C3, low C4, and elevated anti-dsDNA, clinical providers must be diligent in assessing the need for kidney biopsy in SLE: and non-SLE patients as serological activity does not correlate with biopsy findings. Earlier treatment correlates with improved prognosis.

PO1602

Role of Kidney Biopsies in Lupus Erythematosus Patients: Clinicopathologic Correlation
Lorenz Leuprecht, James M. Chevalier, Thangamani Muthukumar, Surya V. Seshan. Weill Cornell Medicine, New York, NY.

Background: Lupus nephritis (LN) affects >50% of the patients with systemic lupus erythematosus (SLE) and is a major cause for morbidity and mortality. The diagnosis of LN as well as the extent and severity of renal involvement are assessed via kidney biopsy. However, appropriate clinical indications for a kidney biopsy are not well defined in adults, nor is the predictability of the clinical presentation. Therefore, a clinicopathologic correlation of patients with SLE and presumed SLE who underwent a kidney biopsy is conducted.

Methods: We evaluated a total of 134 biopsy samples from 123 patients with either SLE or presumed SLE at the time of biopsy that were obtained during a 10-year period at a large medical center in New York City. 11 patients underwent a biopsy twice during that period. Laboratory, and clinical data were also collected retrospectively via chart review.

Results: 86% of the patients were female, 31% African American, 21% White, and 11% Asian. The mean age at the time of the biopsy was 36.2±12.6 years, the mean serum-creatinine 1.45±1.28 mg/dl, and the mean urinary protein excretion 3.86±3.43 g/d. 97% of the biopsy samples had evidence of LN, with the majority showing either Class IV-V (29%) or Class V (33%). About 13% had findings other than LN, such as TMA, focal collapsing features of the glomeruli, diabetic nephropathy, or possible ANCA vasculitis, with or without evidence of LN. Additionally, in patients of 65% of the biopsy samples, eGFR was <60 ml/min/1.73 m², and 29% (38/132) had a negative urine dipstick for blood. Complement levels were low in 88/128 instances, and anti-dsDNA was positive in 57% of patients.

Conclusions: We conclude that normal serum-creatinine values may not preclude significant kidney pathology in SLE patients and those with proliferative forms of LN may have a negative urine test for blood (14%), normal complement levels (14%), and/or a negative anti-dsDNA test (29%) around the time of the biopsy. Furthermore, patients with SLE may have other morphologic findings correlating with clinical renal presentation, instead of LN.

PO1603

Rituximab for Severe Recurrent Proliferative Lupus Nephritis After Kidney Transplantation: Pondering a Rare Case
Rui Song, Mingyue He, Ilay Rahaman, Serban Constantinescu, Iris J. Lee. Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: Severe histologic recurrence of lupus nephritis (LN) post-kidney transplantation (KTX) is extremely rare on standard transplant immunosuppression. Severe recurrence shortens allograft survival, yet treatment guidelines post-KTX are lacking.

Case Description: A 52-year-old African American (AA) man with ESRD secondary to LN underwent a second KTX from a deceased donor. He had a prior living-unrelated KTX with graft failure due to mixed rejection without LN recurrence. For the second KTX, he received Thymoglobulin induction and maintenance immunosuppressive regimens including antithymocyte globulin sodium (ATG), Tacrolimus, Prednisone, with immediate graft function (nadir creatinine 1.4 mg/dL). He developed leukopenia requiring a reduction of EC-MPS to 360mg twice daily. He developed nephrotic range proteinuria 6 months post-KTX but had stable allograft function, bland urine sediment, normal complements, and negative anti-dsDNA antibodies. Despite inactive serologies, allograft biopsy revealed diffuse proliferative sclerosing and crescentic LN (ISN/RPS class IV). Due to persistent leukopenia, Rituximab was chosen over commonly-used Cyclophosphamide (CYC) for therapy. He received intravenous Methylprednisolone (3000 mg) and Rituximab 800mg (375 mg/m²) for 4 doses. Complete B-cell depletion was maintained for 3 months. His proteinuria decreased from 6.9 g/d to 1.2 g/d, and renal allograft function remained stable.

Discussion: Severe recurrent LN post-kidney transplantation is rare and can present atypical serologic markers, bland urine sediment and lack of LN recurrence on the first KTX did not rule out LN recurrence on the second kidney allograft. In our case, only the presence of persistent progressive proteinuria warranted allograft biopsy. AA ethnicity and reduction of EC-MPS were risk factors, which highlights the significance of KTX pathogenesis. Rituximab targets CD20+ B cells and has been successfully utilized for refractory LN. It has a more favorable toxicity profile compared to CYC which has been the conventional treatment for clinically significant LN post-KTX. We propose Rituximab as a better treatment option for severe recurrence of LN post-KTX.

PO1604

Influenza Vaccination in Systemic Lupus Erythematosus (SLE): Effectiveness, Efficacy, Safety, Utilization, and Barriers
Loo Lin Sing,1 Cybele S. da Cunha,1 Monica M. Seshan.1 1Singapore General Hospital Singapore Yong Loo Lin School of Medicine, Singapore, Singapore, 2Singapore General Hospital, Singapore, Singapore.

Background: Influenza infections increase morbidity and mortality among immunocompromised individuals with SLE and lupus nephritis. Yet, they are highly preventable through vaccination. We aimed to describe the effectiveness, efficacy, safety, utilization and barriers to influenza vaccination in SLE so that targeted strategies can be implemented to improve vaccination rates.

Methods: We conducted a systematic review and meta-analysis of all published and unpublished studies up to 19 May 2021 via PubMed, Embase, Cochrane, WHO Clinical Trials, and ClinicalTrials.gov, which reported on our desired outcomes relating to influenza vaccination in SLE and lupus nephritis.

Results: Of 726 articles screened, 44 studies (14779 patients) were included. 9 studies reported on effectiveness, 20 studies on efficacy, 24 studies on safety, 12 studies on utilization, and 4 studies on barriers to influenza vaccination. Involvement or lupus nephritis was present in 20.5%. The majority were female (90.8%). The mean age was 41.3 years (95% CI 36.8-45.7), mean disease duration was 10.91 years (95% CI 7.10-14.72), and mean SLEDAI score was 4.15 (95% CI 3.18-5.12). Individuals who received influenza vaccination were less likely to develop pneumonia (relative risk, RR 0.38, 95% CI 0.08-1.86, p=0.23), acute bronchitis (RR 0.21, 95% CI 0.09-0.48, p=0.0002), and viral respiratory infections (RR 0.36, 95% CI 0.21-0.64, p<0.0005). Pooled seroconversion and seroprotection rates were 56.6% and 68.2% for H1N1, 56.7% and 73.7% for H3N2, and 46.8% and 69.9% for B influenza strains. Mean SLEDAI scores did not change significantly after vaccination. Flares occurred in 20.3%, while local and systemic adverse events occurred in 20.5% and 26.6%, respectively. Only 39.1% of SLE patients were currently vaccinated against influenza. Meta-regression showed that vaccination rates were significantly associated with increasing GDP of the country (p=0.002) and increasing events occurred in 20.5% and 26.6%, respectively. Only 39.1% of SLE patients were currently vaccinated against influenza. Meta-regression showed that vaccination rates were significantly associated with increasing GDP of the country (p=0.002) and increasing

Conclusions: Influenza vaccination is effective and safe in SLE and lupus nephritis. Targeted strategies are required to overcome barriers to improve influenza vaccination uptake.

PO1605

Lupus Nephritis in a Patient with Autoimmune Hepatitis: A Case Report
Soo H. Kang, Erin Lawler, Sankar N. Niranjana.1 UConn Health, Farmington, CT, 2Greater Hartford Nephrology, Bloomfield, CT.

Introduction: Overlapping of autoimmune hepatitis (AIH) and lupus nephritis (LN) is a rare entity, only occurring in 1-2.6% of AIH cases, and is difficult to diagnose due to the overlap of clinical symptoms. Overlapping reports have been revisited in the literature.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO1606**

Delayed Clinical Manifestation of Biopsy-Proven Thrombotic Microangiopathy in a Patient with Lupus Nephritis: A Case Report

Najia Idrice,1 Madeline A. Dilorenzo,1 Joshua S. Hundert,2 Jean M. Francis,1 Hann Menn-Josephy.1 1Boston Medical Center, Boston, MA; 2South Shore Hospital, Weymouth, MA.

**Introduction:** Complement-mediated thrombotic microangiopathy (c-TMA) involves unregulated complement activation due to inherited or acquired mutations in complement regulatory proteins. Immune complex formation, an important component of lupus nephritis (LN) pathogenesis, can over activate the complement system leading to c-TMA in the kidneys. Findings of c-TMA in LN patients have been associated with end-stage kidney disease (ESKD) or death in up to 50% of patients.

**Case Description:** 32-year-old female, with a history of lupus and ISN/RPS class III LN since 2017 and recent stroke, was evaluated at our lupus clinic for LN flare with worsening kidney function, increased proteinuria and low complements. A repeat kidney biopsy showed focal proliferative and membranous LN (ISN/RPS class III and V) and c-TMA. She received standard of care treatment for LN with methylprednisolone and cyclophosphamide, due to past mycophenolate therapy failure. Kidney function and proteinuria improved and complement levels normalized. Three weeks later, she was admitted with hemorrhagic shock secondary to renal subcapsular hematoma stabilized with PRBC transfusions. After one week, she again developed worsening anemia, worsening thrombocytopenia and oliguric acute kidney injury with diuretic resistant anasarca prompting intubation and initiation of hemodialysis. Hemolysis panel revealed a low haptoglobin, high LDH and schistocytes on peripheral smear. Serum complements were low. Due to high suspicion of c-TMA, she received weekly eculizumab followed by eculizumab every 2 weeks. Three weeks later, her hemoglobin and platelets improved and LDH decreased. Her urine output improved and she was able to come off of hemodialysis. She remained with stage 3b CKD.

**Discussion:** In patients with LN, severe renally-limited TMA can present without systemic manifestations. In our patient, hematologic signs of TMA appeared only 4 weeks after her initial biopsy-proven TMA, and after clinical improvement of her LN. This highlights the importance of monitoring LN patients with asymptomatic renally-limited TMA. We hypothesize that they may present with clinical features of active TMA. Anti-complement therapy with eculizumab is shown to be effective in these patients.

**Conclusions:** Despite the majority of patients receiving treatment, a significant proportion (44%) still reached the primary outcome of death or ESKD. Novel and efficacious treatment options are therefore needed to improve the outcomes and prognosis of patients with such a debilitating condition.

**PO1608**

Clinical Characteristics and Outcomes of Severe ANCA-Associated Renal Disease in a Multiethnic Urban Population

Allison J. Leonard,1 Shilpa Arora,2 Ambirath Avathale.1 1John H Stroger Hospital of Cook County, Chicago, IL; 2 Rush University Medical Center, Chicago, IL.

**Background:** To study the clinical characteristics, treatment and outcomes of ANCA vasculitides patients in an inner-city county hospital.

**Methods:** Retrospective study of 60 patients with biopsy-proven ANCA glomerulonephritis and a minimum follow-up of 6 months (median, IQR 23, 29 months) were included. Demographic and clinical information including pathology data, treatment and outcomes were collected. Multivariate regression analyses were done to study predictors of outcomes of estimated Glomerular Filtration Rate (eGFR) at 6 months and End Stage kidney Disease (ESKD).

**Results:** Patients represented an ethnically diverse population (Figure 1) with baseline characteristics as shown in Table 1. Mean age (SD) at diagnosis was 57.4 (13.7). Almost all patients (59/60, 98.3%) presented with hematuria and 17/60 (28.3%) had nephrotic-range proteinuria. Extra renal involvement most commonly pulmonary was seen in 35/60 (58.3%) patients. 44/60 (73.0%) had crescents and nearly all had interstitial fibrosis and tubular atrophy (IFTA) (median, IQR 30%, 56%). Most patients were induced with cyclophosphamide (49/60, 81.7%) and 16/60 (26.7%) received plasma exchange. eGFR (meanSD) at baseline and 6 months follow up were 20.8±19.4 and 43.5±23.0 respectively. 15/60 (25%) patients progressed to ESKD. On multivariate linear regression analysis, age (B -0.5), IFTA (B -27.7) and baseline eGFR (B 0.3) predicted eGFR at 6 months and IFTA (OR, 95% CI, 11.5, 1.1-11907.7) and eGFR at 6 months (OR 0.9, 95% CI 0.8-1.0) were associated with ESKD (P >0.05) on multivariate logistic regression analysis. Ethnicity, ANCA type or titer, crescents on biopsy and treatment received did not predict ESKD at 6 months or ESKD.

**Conclusions:** In this cohort of patients with severe ANCA glomerulonephritis IFTA and baseline eGFR were the most significant predictors of eGFR at 6 months follow up which in turn was associated with progression to ESKD.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO1609

Long-Term Outcome in Patients with ANCA-Associated Vasculitis (AAV): The Monocentric Experience of Brescia

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Background: Renal involvement in AAV is common, ranging between 80 and 90%; of note, up to 40% of patients (pts) with renal involvement will develop End-Stage Renal Disease (ESRD). We explored prognostic factors of renal and overall long-term survival in AAV pts with renal involvement.

Methods: Monocentric, retrospective study, including all pts with clinical or histological diagnosis of AAV with renal involvement followed at our Unit from 1990 to 2019, with follow-up (fu) ≥12 months.

Results: We identified 281 patients. Median fu was 75 months (IQR 33.1-141). Most pts were classified as MPA (71%), followed by GPA (26%) and eosinophilic granulomatosis with polyangiitis (3%). ANCA were positive in 97% (anti-MPO in 66%, anti-PR3 in 31%). At onset, median creatinine was 3.5 mg/dL (IQR 1.9-6.7) and proteinuria 1.1 g/24h (IQR 0.5-2.3). 20% of pts required haemodialysis (HD), with subsequent recovery of renal function in 55% of them. Induction therapy consisted of oral corticosteroids for all pts, along with CYC or RTX. The MCCS stratified renal outcomes for each MCCS grade and can be used as a means for treatment strategy adjustments.

Conclusions: Despite several therapeutic advances, AAV with renal involvement are still characterized by poor prognosis, especially in pts requiring HD at onset and of older age; infection, CV diseases and malignancies were the main causes of death.

PO1610

Predicting Outcomes in ANCA-Associated Vasculitis Using a Complete National Cohort

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Background: Outcomes in ANCA vasculitis remain difficult to predict & therapeutic decision-making can be challenging. We aimed to establish if a renal risk score (RRS) could predict outcomes.

Methods: The Scottish Renal Biopsy Registry is a complete national dataset of all biopsies performed in Scotland. Those who had a first renal biopsy between 2014 & 2017 with evidence of ANCA vasculitis were included. Demographic data & outcomes were recorded. RRS was calculated. Each patient was categorised according to % of normal glomeruli, % of tubular atrophy/intestinal fibrosis & eGFR (CKD-EPI) at time of biopsy. Individual scores were summed & patients defined as low, medium or high risk. Cox proportional hazard models were created for survival to ESRD, relapse & death, stratified by risk group.

Results: Two-hundred & forty-six patients with biopsy proven ANCA vasculitis were identified. Fifty percent (n=123), 46% (n=112) & 8% (n=11) were stratified as low, medium, or high risk, respectively. Most deaths were due to infections (33%), followed by cardiovascular (CV) diseases (20%) and malignancies (13%). At multivariate Cox regression analysis, age; infection, CV diseases and malignancies were the main causes of death.

PO1611

ANCA-Associated Crescentic Glomerulonephritis (AAV-GN) in Patients with Chronic Lymphocytic Leukemia (CLL): A Case Series


Background: Previous case reports have identified an association between CLL and AAV-GN. However, information on the clinical and pathologic characteristics and long-term outcomes of AAV in these patients is rare.

Methods: We queried medical records and research databases of CLL and AAV subjects seen at our institution to identify patients with diagnoses of CLL and AAV-GN from 1990-2020. We analyzed patient demographics, AAV-GN, CLL specific characteristics, treatments, and outcomes. Kidney biopsies were also reviewed.

Results: We identified 12 patients with AAV-GN and CLL. The mean age at diagnosis was 65 years (48, 80) for CLl and 67 years (37, 90) for AAV-GN. 7 patients were diagnosed with CLL prior to AAV-GN, 4 the same month, and 1 developed AAV-GN >3 years after CLL. At the time of AAV-GN diagnosis, all had acute kidney injury, with a median serum creatinine (Scr) of 1.9 mg/dL (SD 3.2). Other organs involved included lungs (n=3), skin (n=1), and eyes/encephalitis (n=1). 9 patients p-ANCA-MPO and 2 had c-ANCA-PR3 and one with an indeterminate ANCA but had PR3. On light microscopy, all had crescents, no vasculitis of the arteries, but 9 patients had focal lymphoid infiltrates without a formal diagnosis of CLL in the kidneys. On immunofluorescence 6/12 had trace to 1+ of IgA, 5/12 with IgG and 4/12 with C3. 5/12 of the biopsies had mesangial deposits and majority (1 with diffuse and 7 with mild–moderate) had foot process effacement. All patients received treatment for AAV (9 with rituximab, and 3 with cytotoxic drugs). Renal outcomes were favorable with 11 patients showing an improvement or stabilization in Scr. One patient (p-ANCA MPO) had high Scr and was managed with HD. All patients lived with both conditions for at least 1 year. We identified 5 patients with both AAV-GN and CLL, the vast majority had p-ANCA MPO, suggesting that the two conditions have either a common underlying lymphocyte dysfunction or that AAV-GN is a predisposing factor to the development of AAV. Anti-CD20 monoclonal antibody therapy was most commonly used, and it led to remission of AAV-GN.

PO1612

Kidney Biopsy Chronicity Grading in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Kidney biopsy is valuable for prognostic assessment of renal outcomes in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with glomerulonephritis (AAV-GN) but the impact of chronic changes is not determined.

Methods: A retrospective cohort study of MPO- or PR3-ANCA positive patients with AAV and active renal disease. We applied the Mayo Clinic Chronicity Score (MCCS), validated and evaluated its implications on outcome prediction in AAV-GN.

Results: We analyzed 329 patients with kidney biopsies available to score. The extent of chronicity was graded by MCCS as (i) minimal ~ 10% (31.0%), (ii) mild ~ 106 (32.2%), (iii) moderate ~ 86 (26.1%), and (iv) severe ~ 35 (10.6%). The MCCS grades correlated with the degree of renal function impairment at presentation (mean eGFR 48.3 vs. 29.2 vs. 23.7 vs. 18.5 mg/L/1.73 m², p<0.0001). Higher degrees of the individual components of the MCCS (glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis) were associated with lower median eGFR (p<0.0001) and decreased event free (kidney failure (KF) and death) survival (p=0.002, p<0.0001 and p<0.0001, respectively). Patients AAV-GN with MCCS grades 1 and 2 had a lower renal function recovery than patients with grades 3 and 4 (p<0.0001). Increasing MCCS grades were associated with decreased renal recovery (p<0.001), more frequent events and shorter time to KF (p<0.0001), KF and death (p<0.0001), and death (p<0.0001) from non-renal events. The MCCS stratified renal outcomes for each MCCS grade and can be used in clinical practice as a risk factor for KF prediction (MCCSa4).

Conclusions: Chronic changes on kidney histology independently predict renal function, outcomes and response to treatment in AAV-GN.

PO1613

The Effect of Cumulative UVB Dose on ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) has a relapsing-remitting course but the precise triggers of onset and relapse are unknown. The potential effect of cumulative ultraviolet B (UVB) radiation on disease phenotype and activity, mediated by vitamin D (vitD), has been proposed, given the marked incidence variation of AAV phenotypes and serotypes with latitude. Using a well-validated vitD proxy (cumulative-weighted UVB) as a marker of cumulative vitD exposure, we hypothesized that cumulative vitD exposure may influence AAV disease phenotype and activity.

Methods: 114 patients with biopsy proven AAV were treated with long-term corticosteroids and immunosuppressants. A cumulative vitD proxy (cumulative-weighted UVB) was calculated. The primary endpoint was the cumulative number of relapses over a given period of time. Secondary endpoints included total renal, extrarenal, and extracranial relapse rates. Mann-Whitney ranksum test and Wilcoxon rank sum test were used to compare AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively. The primary endpoint was compared between AAV phenotypes and disease activity, respectively.
UVB dose (CW-D-UVB) at wavelengths that induce vitD synthesis we hypothesized that prolonged periods of low ambient UVB are associated with an increased risk of GPA phenotype and AAV relapse in this subgroup.

**Methods:** The UKIVAS (n=1994) and Irish Rare Kidney Disease (RKD) (n=439) registries were used (total n=2433). Inclusion criteria: i) definite AAV diagnosis, ii) positive proteinase-3 (PR3) or myeloperoxidase (MPO) serology and/or positive histopathology. Logistic regression was used to investigate the relationship between latitude, CW-D-UVB and AAV phenotype/serotype in the entire cohort. A multi-level model was then applied to examine their effect on AAV relapse risk in the RKD subgroup.

**Results:** CW-D-UVB varied across seasons and latitudes. There was no relationship between latitude/CW-D-UVB at disease onset and AAV phenotype/serotype. MPA, MPO-ANCA, older age and rituximab maintenance were protective against relapse. There was no association between CW-D-UVB and relapse risk, even when examining phenotype specific risk (table 1).

**Conclusions:** We found no association between cumulative UVB, a validated vitD proxy, and AAV phenotype, ANCA serotype nor AAV disease activity in a genetically homogeneous cohort. These findings cast doubt on the role of vitD in AAV disease activity.

**Random effects:**

<table>
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<th>Patient ID</th>
<th>OR (95% CI)</th>
<th>p-value</th>
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<td>CW-D-UVB</td>
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</tr>
<tr>
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<td>0.01</td>
</tr>
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<td>0.09</td>
</tr>
<tr>
<td>Gender</td>
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<td>0.13</td>
</tr>
<tr>
<td>MPA-ANCA</td>
<td>0.96</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**N = 689, 284 observations. OR refers to the probability of having an AAV relapse (relative to remission).**

**Cumulative weighted UV index (CW-D-UVB), Standard deviation (SD), Microscope pathologist (MPH), Myeloperoxidase (MPO), Odds ratio (OR), 95% Confidence interval (DS/CI), Athlete profile (AAP).**

**Results:**

- **Acute Kidney Injury (AKI):**
  - Present in 30% of cases
  - Median serum creatinine increased from 1.2 to 2 mg/dL
  - Recovery observed in 70% of cases

**Discussion:**

- UVB exposure is significantly lower in areas with higher latitude, which may contribute to increased AAV relapse risk.
- Further studies are needed to confirm these findings and explore potential interventions to reduce relapse risk.

PO1615

Pauci-Immune Crescentic Glomerulonephritis Associated with Pulmonary Coccidioidomycosis
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**Introduction:** Coccidioidomycosis is an endemic fungal infection in the southwestern United States. There are around 150,000-300,000 cases annually, of which 60% occur in the state of Arizona. Most patients are asymptomatic. 40% have primary pulmonary involvement and present with dyspnea and fatigue. A minority (around 1%) have extrapulmonary dissemination with unknown incidence of renal involvement.

**Case Description:** We report a 70-year-old immunocompetent patient with CKD (baseline creatinine of 1.2 mg/dL) with a recent diagnosis of pulmonary coccidioidomycosis presenting with AKI due to ANCA negative pauci-immune crescentic GN. Our patient was referred to nephrology for worsened renal function, creatinine of 1.7 mg/dL. He was diagnosed with pulmonary coccidioidomycosis 3 months prior and started on fluconazole 400 mg daily. Due to concern for disseminated coccidioidomycosis, underwent a renal biopsy showing minimally active pauci-immune crescentic GN (Fig 1). Complement levels were normal, ANCA immunofluorescence, anti-MPO and anti-PR3 titers were negative.

**Discussion:** This is the third known reported case of pauci-immune crescentic GN associated with coccidioidomycosis, and one of a handful of case reports describing pauci-immune crescentic GN in patients with chronic fungal infections. Our case highlights the importance in understanding the pathogenesis and prognosis of chronic fungal infections and GN.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
and diffuse ATN. As creatinine worsened (peak 2.66mg/dL), mycophenolate (MMF) was added after resolution of bacteremia following iv antibiotics. 1 week after stopping antibiotics, he was readmitted with AKI, nephritic syndrome, and recurrent E. faecalis bacteremia. MMF was stopped and antibiotics restarted with improvement in creatinine (1.40mg/dL) and urine sediment.

Discussion: This is a rare case of PR3-ANCA vasculitis due to E. faecalis endocarditis. A kidney biopsy and high index of suspicion is crucial in diagnosing pauci-immune GN in patients with preexisting vasculitis. Absence of hypocomplementemia raised suspicion for a superimposed process. This case highlights the importance of a careful evaluation in patients presenting with vasculitis despite appropriate treatment of a preexisting vasculitic syndrome.

PO1617

A Rare Case of Crescentic Glomerulonephritis, Diffuse Proliferative Class IV Lupus Nephritis, and Collapsing Glomerulopathy in a COVID, P-ANCA, and Myeloperoxidase-Positive Patient


Introduction: An unusual case of Diffuse Class 4 Lupus nephritis, along with collapsing Glomerulopathy from asymptomatic COVID infection

Case Description: A 42 year old Asian female presented with painless hematuria, anasarca, reduced hearing, and eye redness over a month. She had empiric antibiotics and steroids prior to admission. On admission, she was hypotensive with anasarca. Labs revealed AKI creatinine of 2.5 mg/dl, proteinuria of 11 grams, and serum albumin 1.9 gm/dL. Urine analysis showed dysmorphic RBCs, RBC casts. Ultrasound showed 12 cm kidneys bilaterally. She had normal complements and DS DNA, antinuclear antibodies, lupus anticoagulant, anti-DNAase B, anti-histone, and anticardiolipin antibodies. Chest CT showed bilateral patchy infiltrates. Sputum and blood cultures for bacterial, fungal, and mycobacterial were negative.

Discussion: This is a rare case of diffuse class IV lupus nephritis with normal complements, DS DNA, and full house pattern on IF. She tested positive for COVID. Her labs showed Hgb: 10.4g/dl, WBC: 6780/mm3, MCV: 80fl, MCH: 28pg, MCHC: 33%, platelets: 357,000, Eosinophils 25%, Cr: 0.7mg/dl, H. Pylori: Positive. Guaic negative. Stool negative for ova/parasites. Endoscopy showed non-blooding erosive gastropathy with scattered punctate ulcerations in the duodenum. On biopsy diffuse acute and chronic inflammation, focal cryptitis, erosion of mucosa, Schistosoma Mansoni ova in glands of stomach, duodenum and jejunum were noted. CT brain negative for cysticercosis. CT chest showed calcified granulomas in right middle lobe and right lower lobe. On reevaluation she admitted to consuming snails. Rituximab maintenance therapy was not continued because of schistosomiasis. She was admitted for a multidisciplinary approach. Renal function remained stable protein/creatinine ratio 0.8, Myeloperoxidase positive . Patient was started on Praziquantel 1.2 g tid and prednisone 60 mg for 5 days which was followed by another cycle after 4 weeks to treat any remaining adult schistosomes. Repeat EGD and colonoscopy with multiple biopsies to ensure eradication of schistosomiasis before resuming rituximab is planned.

Discussion: Our case emphasizes the need to consider parasitic infections when starting patients from endemic areas on immunosuppressive therapy. Schistosomiasis can involve multi-organ systems and can lead to potentially debilitating and fatal complications such as liver fibrosis, portal hypertension, hypersplenism, esophageal variceal bleeding, GN and nephrotic syndrome. Detailed history for dietary habits and lifestyle is important. Serology, antigen detection or other diagnostic tools can be used when the suspicion is high.

PO1618

Schistosomiasis in a Patient on Rituximab for ANCA-Associated Glomerulonephritis

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Introduction: Rituximab and glucocorticoids induce remission in ANCA associated vasculitis with renal involvement. Rituximab induces B-cell depletion and influences T-cell immunity, which predisposes patients to serious infectious complications. We present a case of schistosomiasis in a patient on rituximab for Pauzi Immune Glomerulonephritis (GN) associated with ANCA vasculitis.

Case Description: A 39 years old female from Honduras with history of sero-negative arthritis, acute kidney injury with pauci immune, focal necrotizing and diffuse crescentic GN on kidney biopsy and P-ANCA positive, was treated on rituximab and glucocorticoids. Ten months later, while in remission she presented with nausea, vomiting, obstipation and abdominal pain. Her labs showed, Hgb: 10.4g/dl, WBC: 6780/ mm3, Eosinophils 25%, Cr: 0.7mg/dl, H. Pylori: Positive. Guaic negative. Stool negative for ova/parasites. Endoscopy showed non-blooding erosive gastropathy with scattered punctate ulcerations in the duodenum. On biopsy diffuse acute and chronic inflammation, focal cryptitis, erosion of mucosa, Schistosoma Mansoni ova in glands of stomach, duodenum and jejunum were noted. CT brain negative for cysticercosis. CT chest showed calcified granulomas in right middle lobe and right lower lobe. On reevaluation she admitted to consuming snails. Rituximab maintenance therapy was not continued because of schistosomiasis. She was admitted for a multidisciplinary approach. Renal function remained stable protein/creatinine ratio 0.8, Myeloperoxidase positive . Patient was started on Praziquantel 1.2 g tid and prednisone 60 mg for 5 days which was followed by another cycle after 4 weeks to treat any remaining adult schistosomes. Repeat EGD and colonoscopy with multiple biopsies to ensure eradication of schistosomiasis before resuming rituximab is planned.

Discussion: Our case emphasizes the need to consider parasitic infections when starting patients from endemic areas on immunosuppressive therapy. Schistosomiasis can involve multi-organ systems and can lead to potentially debilitating and fatal complications such as liver fibrosis, portal hypertension, hypersplenism, esophageal variceal bleeding, GN and nephrotic syndrome. Detailed history for dietary habits and lifestyle is important. Serology, antigen detection or other diagnostic tools can be used when the suspicion is high.
protocol and Rituximab therapy per the RAVE trial protocol. Cr improved (1.6 mg/dL) after induction therapy with persistent mild proteinuria at <500 mg/g at 6 months. Dual MPO and PR3 positivity persisted until Rituximab completion, after which only MPO positivity continued.

**Discussion:** It is well known that anti-thyroid medications can cause drug-induced AA V. However, this renal limited AA V case with desiccated thyroid supplementation suggests clinicians should also be aware of AA V as a possible adverse consequence of thyroid supplementation. Management should include discontinuation of the offending agent and consideration of immunosuppression with standard induction regimens based on disease severity.

**PO1620**

**Renal Survival in Anti-Glomerular Basement Membrane Disease**

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**Background:** Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated kidney disease. Presentation with severe kidney dysfunction in need of renal replacement therapy (RRT) often results in end stage kidney disease (ESKD).

Reliable predictors of kidney survival are needed.

**Methods:** Retrospective analysis of patients with anti-GBM disease from the North West of England.

**Results:** Seventy patients with GBM nephritis were identified, 20 patients presented double positive for anti-neutrophil cytoplasmic antibodies (ANCA) and GBM antibodies (28.57%). Median age was 64 years (Interquartile range 43 – 76 years). 39 patients were female (55.7%). Median kidney function at presentation was an estimated glomerular filtration rate of 93 ml/min (eGFR, IQR 41.95 – 83.55 ml/min). Sixty patients required RRT at presentation, and twelve of these patients recovered sufficient kidney function to withdraw RRT (25.5%). Median follow up was 41 months (IQR 11 – 77.5), and during follow up two additional patients developed ESKD (n = 50). The median presenting eGFR was numerically higher but not significantly different in patients that required dialysis initially and recovered residual function compared to patients that remained dialysis dependent, and no cut-off was detected (p=0.25). Patients with presenting eGFR as low as 2.1 ml/min recovered function.

**Conclusions:** Timely aggressive therapy to salvage kidney function is crucial. Better predictors of outcome are needed to optimise management in GBM vasculitis.

**PO1621**

**Validation of the Renal Risk Score in Anti-GBM Disease**

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**Background:** Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated kidney disease. Presentation with severe kidney dysfunction in need of renal replacement therapy (RRT) often results in end stage kidney disease (ESKD). Clinical and histological variables predicting outcome are needed to identify individual therapy and improve outcome.

**Methods:** We performed a retrospective multicentre analysis and investigated the Renal Risk Score (RRS) proposed in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis for its prognostic value in anti-GBM disease. We used the published cut-offs for percentage of normal glomeruli (N0 > 25%, N1 10 - 25%, N2 < 10%), estimated glomerular filtration rate (eGFR, G0 > 15 ml/min/1.73 m2, G1 15 ml/min/1.73 m2) and a simplified cut off for tubular atrophy and interstitial fibrosis (TA ≤ mild, T1 ≥ moderate, T2 ≥ severe) according to the published RRS. We identified 70 patients with ANCA and GBM antibodies (28.57%). Median age was 64 years (Interquartile range, IQR 43 – 76 years). 39 patients were female (55.7%). Median eGFR at presentation was 93 ml/min (IQR 41.95 – 83.55 ml/min). Median follow up was 41 months (IQR 11 – 77.5), and during follow up two additional patients developed ESKD (n = 50). The median presenting eGFR was 2.1 ml/min.

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**Conclusions:** Timely aggressive therapy to salvage kidney function is crucial. Better predictors of outcome are needed to optimise management in GBM vasculitis.
Ibrituzumab, a Novel Anti-CD6 Antibody, in Systemic Lupus Patients with Glomerular Diseases: Treatment and Outcomes

Preferencias Regarding Treatment with Plasma Exchange for ANCA-Associated Vasculitis: An International Patient Survey

Maintenance Remission and Risk for Relapse in Myeloperoxidase Positive Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Kidney Involvement

Glomerular Diseases: Treatment and Outcomes

POI1625

Adding Low-Dose CYC to RTX Combined with a Tailored RTX Maintenance Regimen Seems to Favor Stable Remission in Severe ANCA Vasculitis

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Background: Rituximab (RTX) and cyclophosphamide (CYC) are effective remission-induction therapies in ANCA-associated vasculitis (AAV). High dose CYC is however considered toxic, whereas RTX monotherapy may increase the risk of relapse, depending on the choice of maintenance therapy and baseline disease severity. Particularly with renal involvement, stable remission will favor prognosis. In this respect, adding low dose CYC to RTX could be superior to RTX alone. We checked this premise by retrospectively analyzing our data derived from a pragmatic, clinical approach in patients with severe AAV.

Methods: Between 2007 and January 2019, 246 patients with severe active AAV, needing remission-induction therapy, were screened and 62 patients were included. Remission-induction consisted of either RTX only (n=7) or RTX-CYC (n=55). Secondary endpoint was major relapse rate and adverse events at 2 and 5 years, compared with the log-rank test.

Results: 28 patients received RTX only and 34 patients received RTX-CYC. Disease presentation, severity of disease (BVAS), and laboratory parameters (serum creatinine, CRP, and IgG) at 20 the UCPR were similar. Baseline UCPCR was more prevalent in the RTX-CYC patients (85.3%) as compared to RTX only (60.7%) (P = 0.028). Relapse rates within 2 years were significantly higher in the RTX only group (n=7 in RTX only, n=1 in RTX-CYC, P = 0.015), however the number of patients receiving RTX maintenance and the number of infusions did not differ. After 5 years, however, relapse rates did not differ (n=9 in RTX only and n=7 in RTX-CYC). The rate of infections, hypogammaglobulinemia, end stage renal disease, malignancies, and mortality did not differ after 2 and 5 years.

Conclusions: Adding low dose CYC to RTX is safe and may favor the prevention of major relapses in patients with severe AAV, predominantly with renal involvement. Future prospective studies are needed to examine the role of reconstituted B cells and ANCA features to better define tailor-made treatment decisions.

POI1626

Preferencias Regarding Treatment with Plasma Exchange for ANCA-Associated Vasculitis (AVE) are uncertain. We sought to elicit patient preferences regarding the use of PLEX in AAV.

Methods: An online survey was circulated via national vasculitis and kidney patient networks. Respondent characteristics were collected and information regarding PLEX in AAV was provided including its minimal effect on mortality. One year incidence of end stage kidney disease (ESKD) and serious infections with and without PLEX in AAV were presented across 5 serum creatinine categories: 150, 250, 350, 450 and 600µmol/L. For each scenario, participants were asked: "If they were a patient with a new diagnosis of ANCA vasculitis, they would choose PLEX (yes or no) given its absolute risk reduction in ESKD, but absolute risk increase in serious infections?" Multilevel multivariable logistic regression was performed to identify independent predictors of choosing treatment with PLEX.

Results: There were 549 responses. The mean age of respondents was 57.4 (SD 14.5) years, 72.3% were female, and respondents were from the United States (58.1%), United Kingdom (23.7%), Canada (14.0%), and other countries (4.2%). The majority had AAV (86.7%). 190/549 (34.6%) would always choose PLEX and 87/549 (15.8%) would always decline PLEX across the baseline risks of ESKD or serious infections presented. Independent predictors for choosing PLEX included age (OR 0.98, 95% CI 0.96-0.99 per 1 year increase), country (United Kingdom OR 2.73, 95% CI 1.20-6.21), diagnosis (individuals with vasculitis other than AAV were more likely), previous dialysis (OR 3.34, 95% CI 1.37-8.16), preference for maintenance strategy (OR 2.50, 95% CI 2.50-10.49), and increased baseline risk of ESKD (Cr 350 and 450µmol/L only).

Conclusions: One third of participants would always choose treatment with PLEX across the 5 scenarios presented. The decision to choose PLEX is influenced by age, country, previous dialysis, and the baseline risk of ESKD and serious infections. Patient values and preferences are needed to inform shared decision-making regarding PLEX in AAV.

POI1627

Maintenance of Remission and Risk for Relapse in Myeloperoxidase Positive Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Kidney Involvement

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Background: Optimal time of remission-maintenance therapy in patients with MPO-ANCA associated vasculitis (MPO-AAV) is not established. Defining clinical and laboratory parameters to guide safe withdrawal of maintenance immunosuppression is required in order to mitigate the risk of relapse.

Methods: A retrospective cohort study of all patients followed at the Mayo Clinic with MPO-AAV (MPA and GPA) and their remission strategy was characterized.

Results: We analyzed 159 MPO-ANCA positive patients with active kidney involvement. A total of 66 (41.5%) patients had at least 1 relapse. MPO-ANCA patients who became and remained seromorfolgic did not relapse (HR 0.03, [95%CI, 0.001-0.970], p=0.048). MPO-ANCA reappearance after seronegative conversion was associated with increased relapse rate at 24 months (HR 3.651, [95%CI, 1.14-11.966]; p=0.012). Immunosuppression was withdrawn in 80 (50.3%) and this was predicted by persistent MPO-ANCA seronegative conversion (OR 3.028, [95%CI, 1.262-7.268]; p=0.031). In patients who withdrew remission-maintenance therapy, 32 (40.0%) relapsed (in comparison with 34 relapses [43.0%] in those who maintained immunosuppression, p=0.097). ENT involvement (OR 6.095 [95%CI, 1.280-29.010], p=0.023) and MPO-ANCA reappearance (OR 9.248, [95%CI, 2.743-27.361], p<0.0001), were independent predictive factors for relapse after withdrawal.

Conclusions: Our results suggest that patients who seroconverted and remain MPO-ANCA negative are at lower risk of relapse: remission-maintenance treatment might be withdrawn without an additional risk of relapse. MPO-ANCA reappearance after seronegative conversion is not a risk factor for relapse at 24 months. Serial MPO-ANCA determinations are useful to guide clinical decisions on remission-maintenance treatment strategies.
PO1628
Renal Histological Biomarkers and Response to Different Induction Regimens in ANCA-Associated Glomerulonephritis: The REASSESS Study
Martina Uzzo, Jennifer Scott, Alice A. Guerini, Stefania Afflato, Rosanna Lacetera, Andreas Kronbichler, Iva Gunnarsson, Marco Allinovi, Gaetano La Manna, Mario Cuzzolin, Annette Bruchfeld, Federica Mescia, Federico Pieruzzi, Stephen P. McAdoo, Renato A. Sinico, Mattia Cmorgone, Francesco Scolari, Mark A. Little, David R. Jayne, Federico Alberici.

Background: The role of kidney biopsy on ANCA-associated vasculitis (AAV) is still debated: despite its significant prognostic value, whether it has an impact on the induction regimen choice has not been explored yet.

Methods: 323 AAV patients with biopsy-proven renal involvement were collected retrospectively from eleven centers and stratified according to the histopathological characteristics at the kidney biopsy and the induction regimen employed.

Results: The median follow-up time was 36 months; the eGFR was 19 ml/min/1.73m². 53% were MPO-ANCA and 41% PR3-ANCA; 58% were treated with Cyclophosphamide (CYC), 18% with Rituximab (RTX) and 24% with RTX-CYC. According to the K-M classification, 24% biopsies were classified as Focal, 31% as Crescentic, 33% as Mixed (CYC), 18% with Rituximab (RTX) and 24% with RTX-CYC. According to the response analysis with the K-M curve, patients in the Crescentic group treated with RTX had a shorter ESRD-free survival compared to the CYC group (p=0.033) and the RTX-CYC one (p=0.044). This was confirmed with a Cox regression analysis adjusted for sex, age, ANCA type, AAV diagnosis, creatinine and proteinuria when comparing the RTX group with the CYC one.

Conclusions: Response rates and relapse rate were comparable in the overall cohort and in each histopathological subgroup. The ESRD-free survival in the Crescentic class was shorter in the RTX group compared to the CYC one.

PO1629
ANCA Vasculitis Induction Management in the COVID-19 Pandemic: Results of an International Retrospective Cohort Study
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Background: Induction therapy for severe ANCA-associated vasculitis (AAV) combines glucocorticoids (GC) with either rituximab (RTX) or cyclophosphamide (CYC). The coronavirus 2019 disease (COVID-19) pandemic has increased concern around using aggressive immunosuppression; whether this concern has impacted AAV management is unknown. Here, we report treatment regimens and outcomes of patients with active AAV receiving induction immunosuppression during the first wave of the pandemic.

Methods: We retrospectively studied AAV patients with new or relapsing disease receiving remission induction therapy during the first wave of the COVID-19 pandemic across sites in the US, UK and Europe. Primary outcome was achievement of complete remission at 6 months.

Results: Of 191 patients with a mean age of 65 years old, 52% were female and a majority (89%) were Caucasian. Standard induction was deployed across all sites. Out of the US, UK, and European patient populations, the US used higher GC pulses leading to a higher average cumulative GC dose for remission induction (4153 mg, 2174 mg, 3400 mg respectively, p<0.001) and had the highest proportion of patients given RTX induction therapy (64%; p=0.005). Complete remission was achieved in 90% of patients. Improvement in kidney function at 6 months was similar with all treatment regimens (6 ml/min² increase, p=0.68). Sixteen patients were diagnosed with COVID-19 and had similar exposures to CYC and RTX. There were no differences in remission rates, ESKD or death when stratified by induction therapy type.

Conclusions: Induction immunotherapy practices differ across the world, but specialists continued their standard management during the COVID-19 pandemic. AAV outcomes or rates of COVID-19 infection were not influenced by different induction regimens.

PO1630
Non-Sucrose Containing IV Immunoglobulin in ANCA Vasculitis Has No Adverse Effects on Renal Function
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Background: Intravenous immunoglobulin (IVIG) has proven to be effective as an immunomodulator in several autoimmune and inflammatory diseases, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Moreover, in the era of B cell-depleting therapies, secondary immunodeficiencies are common, urging supplementation by IVIG. Reported adverse effects are generally mild in nature. However, concerns have been raised about the safety profile of IVIG in relation to renal function. IVIG associated kidney injury is proposed to be mainly related to sucrose stabilized products. Non-sucrose containing alternatives are available and increasingly used. We therefore aimed to analyze the safety of non-sucrose containing IVIG with regard to renal function in patients with AAV.

Methods: AAV patients of the Maastricht University Medical Center were retrospectively analyzed for dynamics of serum creatinine levels before and after IVIG using the Wilcoxon signed rank-test. Subanalyses were performed with regard to the presence of ANCA-associated renal disease and IVIG indication. In addition, correlation analysis was conducted to evaluate the relation between serum creatinine change and cumulative IVIG dose during a 1-year follow-up.

Results: 36 with 49 courses of IVIG were included in the short-term and 54 patients with 70 courses of IVIG were included in the long-term analysis. No significant differences were found between serum creatinine levels before and after IVIG in the short-term (median [IQR], 32 [28-39] and 32 [28-39] mmol/L, P=0.60), with a median follow-up of 16 days after the initial IVIG infusion, and the long-term (median [IQR], 110 [90-135] and 110 [90-152] mmol/L, P=0.077), after a year. One patient with active AAV and renal involvement had a reversible serum creatinine increase >30% 6 days after IVIG. Subanalyses showed no significant changes in serum creatinine levels with regard to renal involvement and IVIG indication. There was no association between serum creatinine change and cumulative IVIG dose 1 year after the initial IVIG infusion (P=0.667).

Conclusions: This study shows no short-term and long-term deleterious effects on renal function in response to treatment with non-sucrose containing IVIG in patients with AAV.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1631

Efficacy and Safety of a Combination Treatment of Mycophenolate Mofetil and Corticosteroid in Advanced IgA Nephropathy: A Multi-center, Prospective Study
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Background: It remains unclear whether immunosuppressive agents are effective in patients with IgA nephropathy (IgAN). We sought to determine the efficacy of mycophenolate mofetil (MMF) and corticosteroid combination therapy in patients with advanced IgAN.

Methods: We conducted a multicenter, randomized, placebo-controlled, parallel group study of a 48-week administration of MMF and corticosteroids in biopsy-proven advanced IgAN patients with an estimated glomerular filtration rate (eGFR) between 20-50 mL/min/1.73m² and a urine protein-to-creatinine ratio (UPCR) greater than 0.75g/day. The primary outcome was complete (UPCR<0.3g/day) or partial remission (reduction of UPCR >50%) compared to baseline at 48 weeks.

Results: Of the 48 randomized patients, complete and partial remission rates were higher in the MMF and corticosteroid combination therapy group (29.1% vs. 5.0%, P<0.05). In contrast to the combination therapy group, eGFR in the control group significantly decreased from 36 weeks onwards, resulting in a final adjusted mean change of -4.39 ± 1.22 mL/min/1.73m² (P<0.002). The adjusted mean changes at 48 weeks were 0.62 ± 1.30 and -5.11 ± 1.30 mL/min/1.73m² (P=0.005) in the treatment and control groups, respectively. The amount of UPCR was also significantly different between the two groups, where the adjusted mean change was -0.47 ± 0.17 mg/mgCr in the treatment group and 0.07 ± 0.17 mg/mgCr in the control group (P=0.04). Overall adverse events did not differ between the groups.

Conclusions: In patients with advanced IgAN with a high risk for disease progression, combination therapy of MMF and corticosteroid appears to be beneficial in reducing proteinuria and preserving renal function.

POI1632

Pharmacodynamic and Clinical Responses to BION-1301 in Patients with IgA Nephropathy: Initial Results of a Ph1/2 Trial
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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally, with up to 45% of patients at risk of progressing to ESKD. The initiating step in IgAN pathogenesis is the excessive production of galactose-deficient IgA1 (Gd-IgA1), resulting in the formation of immune complexes that cause kidney inflammation and damage. A Proliferation-Inducing Ligand (APRIL) is elevated in IgAN patients and correlated with higher levels of Gd-IgA1 and proteinuria, and lower eGFR.

BION-1301 is a novel monoclonal antibody targeting APRIL. Here we present interim results from Part 3 of a Phase 1/2 study that characterizes the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary activity of BION-1301 delivered by IV administration in patients with IgAN.

Methods: Part 3 of this Phase 1/2 study (NCT03945318) is an ongoing multicenter, multicohort, open-label study in up to 40 IgAN patients. In Cohort 1, BION-1301 is dosed at 450mg IV every 2 weeks for up to 12 months. Key objectives of the study include safety and the characterization of PK, PD, immunogenicity and changes in proteinuria. Key eligibility criteria include: (1) urine protein ≥0.5 g/24h or baseline UPCR ≥0.5 g/g, (2) stable/optimized dose of ACE-I/ARB or ACE-I/ARB intolerant and (3) biopsy-verified diagnosis of IgAN within the past 10 years.

Results: Preliminary results from the first 5 patients show BION-1301 is well tolerated with no serious adverse events and no adverse events leading to discontinuation to date. BION-1301 drives durable reductions in serum free APRIL, Gd-IgA1, IgA and IgG with a lesser reduction in IgM. A clinically meaningful reduction of UPCR was observed within 3 months. Updated data in all 46 treated patients, along with mechanistic response kinetics, will be presented at the meeting.

Conclusions: BION-1301 is a novel anti-APRIL monoclonal antibody being developed for potential therapy for patients with IgAN. BION-1301 treatment was modifying potential by directly targeting the pathogenesis of IgAN. Promising early biomarker and clinical activity support the continued development of BION-1301 in IgAN.

Funding: Commercial Support - Chinook Therapeutics

POI1634

Atrasentan Exhibits a Consistent, Predictable Pharmacokinetic Profile Among Healthy Asian Adults
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Background: Atrasentan, a potent and selective endothelin-A receptor antagonist, is under investigation for reducing proteinuria and preserving kidney function in IgA nephropathy and other glomerular diseases. Two phase 1 studies evaluated the pharmacokinetics (PK) and safety of atrasentan in healthy adults of Chinese (Study M11-521) and Japanese (Study M11-522) parentage.

Methods: Study M11-521 was an open-label, randomized (for single-dose regimens), single-center study of single and multiple doses of atrasentan in 36 healthy Chinese adults. Single doses of atrasentan tablets (0.5, 1, or 1.5 mg) were administered in Part I, and multiple dose studies of atrasentan 1.5 mg were administered in Part II. Study M11-522 was a double-blind, randomized, placebo-controlled, single-center study of single doses of atrasentan (0.5, 0.75, or 1.25 mg) in 36 healthy Japanese adults. Blood samples were collected for analysis of plasma PK parameters, including the area under the plasma concentration-time curve (AUC) and the maximum observed plasma concentration (Cmax).

Results: In Study M11-521, atrasentan AUC increased proportionally with dose in the 0.5 mg to 1.5 mg dose range, and Cmax increased proportionally with dose in the 1 mg to 1.5 mg dose range. No statistically significant differences were observed in either the dose-normalized AUC or for the comparison of the 1.5 mg and 0.5 mg dose groups (P = 0.260) or the dose-normalized Cmax, for the comparison of the 1.5 mg and the 1 mg dose groups (P = 0.279). In Study M11-522, a linear increase in atrasentan mean AUC, was observed across the 0.5 to 1.25 mg dose range; dose-normalized mean Cmax did not show a statistically significantly different across the doses (P = 0.735). Atrasentan was generally well tolerated. No clinically significant vital signs, electrocardiogram activity, or laboratory measurements were observed, and no apparent significant differences among the dose regimens were found with respect to safety.

Conclusions: Dose-proportional increases in AUC were observed across the studied range, which includes the 0.75 mg dose being studied in ongoing clinical trials. These data support the safety and tolerability of atrasentan and suggest a consistent and predictable PK profile among patients of Asian descent.

Funding: Commercial Support - Abbvie, Chinook

POI1634

Randomized Clinical Study to Evaluate the Effect of Personalized Therapy on Patients with Immunoglobulin A Nephropathy (IgAN)
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Background: IgA nephropathy is known to be a highly heterogeneous disease, with patients having different disease severities, treatment responses, and outcomes. Personalized therapy is critical to optimize clinical outcomes and reduce treatment-related complications.

Methods: Our clinical study of IgAN (CLIgAN) is a multicentre, prospective, controlled and open-label randomized clinical trial based on patient’s stratification at the time of their kidney biopsy. The trial has been registered in ClinicalTrials.gov (NCT 04662723). We will consider, first, the type of renal lesions followed by serum creatinine values, GFR and proteinuria. Primary and secondary end points have been established. Second, we will determine whether personalized therapy can slow the decline of the renal function and delay the ESKD.

Results: We will enroll 132 IgAN patients with active renal lesions (66 patients per arm) in the first RCT (ACLigAN). They will receive corticosteroids combined with renin-angiotensin system blocker (RASB) or RASB alone. Two hundred ninety-four IgAN patients with chronic renal lesions at high or very high risk of chronic kidney disease (147 patients per arm) will be enrolled in the second RCT (CHRONIgAN) in which they will receive sodium-glucose cotransporter -2 inhibitor (SGLT2-i) combined with RASB or RASB alone.
Conclusions: Using this approach we hypothesize that patients could receive personalized therapy based on renal lesions to ensure that the right drug gets to the right patient at the right time.

Funding: Private Foundation Support

PO1635
Enhanced Efficacy of Corticosteroid Therapy by Tonsillectomy in IgA Nephropathy
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Background: Efficacy of corticosteroid therapy in IgA nephropathy may vary among countries or races. Nowadays, the strategy to enhance efficacy of corticosteroid therapy is desired. In 2014, our randomized controlled trial demonstrated that corticosteroid therapy combined with tonsillectomy had superior anti-proteinuric effect than that of corticosteroid therapy alone (Nephrol Dial Transplant. 2014). However, the benefit of combining corticosteroid therapy with tonsillectomy for long-term renal survival was uncertain. Therefore, in a Japanese nationwide prospective cohort dataset, we aimed to evaluate whether the benefit of corticosteroid therapy may increase when it was combined with tonsillectomy, or not.

Methods: Patients were registered between April 1, 2005 and August 31, 2015 at 44 facilities throughout Japan. The primary outcome was a 50% increase in serum creatinine from baseline or dialysis initiation. Two interventions were focused in the present study: corticosteroid with or without tonsillectomy. Survival analysis was adjusted with baseline clinicopathological parameters including eGFR, proteinuria, hematuria, RAS inhibitor use and MEST-C score in Oxford classification.

Results: Enrolled 991 patients showed 75.4 ml/min as mean eGFR and 0.58 g/day as median level of proteinuria. Among them, 634 (64.0%) and 425 (42.9%) patients received corticosteroid therapy and tonsillectomy, respectively. During the median follow up of 5.5 years, 87 patients (8.8%) reached primary outcome. Adjusted hazard ratio (HR) of corticosteroid therapy for primary outcome in patients with tonsillectomy was 3-fold favorable than that in those without tonsillectomy (HR 0.18, 95% confidence interval [CI] 0.06-0.65, versus HR 0.59, 95%CI 0.34-1.01; P value for interaction between corticosteroid therapy and tonsillectomy 0.060).

Conclusions: Enhanced efficacy of corticosteroid therapy by tonsillectomy in IgA nephropathy was confirmed in a Japanese nationwide prospective cohort.

Funding: Government Support - Non-U.S.

PO1636
The Potential Role of Monthly Corticosteroid Pulse in IgA Nephropathy
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Background: The risk of corticosteroid therapy may be underestimated in IgA nephropathy (IgAN). Previous studies provided that a fifth part of patients was older than 60 years and the rate of diabetes mellitus (DM) was increased in IgAN. The novel corticosteroid therapies with not losing benefit and reduced risk of corticosteroid are desired. Here, we aimed to determine whether monthly corticosteroid pulse is inferior in proteinuria remission and superior in blood glucose control to standard corticosteroid therapy or not.

Methods: Design: Retrospective, non-inferiority study. Participants: Adult patients with IgAN received intervention described below between 2013 and 2020. Intervention: Monthly corticosteroid pulse alone for 6 months versus standard corticosteroid therapy having oral corticosteroid for 6 months and three times of pulse corticosteroid in the same 6 months (Lancet 1999). Outcomes: The primary outcome was proteinuria remission (<0.3g/day) at 1 year and we prespecified 0.67 in odds ratio (OR) as non-inferiority margin. The secondary outcome was safety of blood glucose care, which was defined by glucose level by 1 quartile, atacicept 25 mg stably reduced Gd-IgA1 levels by 1 quartile in 2/6 group had significant reductions. PBO pts transiently increased or decreased Gd-IgA1 levels by 1 quartile all 3 of 3 in the PBO group did not reach the statistical requirements for a proven non-inferiority on proteinuria remission, but significantly exhibited safety outcome in the control of blood glucose. Prospective larger studies are needed to determine the role of monthly corticosteroid pulse in IgAN.

PO1637
The Beneficial Effects of Renin-Angiotensin System Inhibitors on IgA Nephropathy with Global Sclerosis
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Background: In IgA nephropathy (IgAN), global sclerosis has been recognized as one of the risk factors for progression, because it induces glomerular hypertension and hyperfiltration in the remained glomeruli. The reno-protective effects of renin-angiotensin system inhibitors (RASI) are considered to decrease glomerular hypertension and hyperfiltration, but their effectiveness in IgAN with global sclerosis has been unknown.

Methods: Of the 871 IgAN patients diagnosed at our institution, we classified them into three grades by the ratio of global sclerosis (G) against whole glomeruli (G0 (n=225): none, G1 (n=445): at least one but <25%, G2 (n=191): ≥25%). We compared each clinical background and 20-year prognosis. Then, we examined the effect of RASI initiated during follow-up period on the long-term prognosis in patients with G1+G2 and in patients with G2 by Kaplan-Meier analysis and Cox regression analysis. To adjust the background characteristics between patients treated with or without RASI, propensity matching score was performed.

Results: The age, blood pressure, proteinuria, renal function, and histological findings were significantly severer with increasing grade in G0, G1, and G2, and 20-year renal survival rate was 83.5%, 75.0% and 54.4% in patients with G0, G1, and G2, respectively (p<0.001). After propensity matching between patients treated with or without RASI, 366 patients in G1+G2 and 90 patients in G2 were eligible for the evaluation. The 20-year renal survival rate was significantly higher in the patients with RASI than in the patients without RASI (G1+G2: 84.5% vs. 59.0%, p<0.001, G2: 63.8% vs. 33.5%, p=0.037). In multivariate Cox regression analysis considering clinical and histological findings and treatment, RASI was an independent factor to prevent progression in patients with G1+G2 and G2 (G1+G2, hazard ratio: 0.39, 95% confidence interval: 0.25-0.62, p<0.001; G2, hazard ratio: 0.35, 95% confidence interval: 0.19-0.66, p<0.001).

Conclusions: In this study, global sclerosis was associated with severer clinical and histological findings, and poor prognosis. However, RASI initiated during follow up period was found to improve renal prognosis in IgAN with at least one global sclerosis.
PO1639

Remission of IgA Nephropathy with Hydroxychloroquine

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Introduction: IgA nephropathy is the most common form of glomerulonephritis in the world. Treatment options include blockade of renin-angiotensin-system (RAS) as the first line of therapy. Steroids may be beneficial in refractory cases, however, can result in several adverse effects. Data regarding use of immunosuppression is inconclusive. Combination of RAS inhibition and hydroxychloroquine has shown to reduce proteinuria in recent studies, though, complete remission with long term use has not been described. We report the case of a 46-year-old Asian female with IgA nephropathy, who was treated with maximally tolerated RAS inhibition and hydroxychloroquine for about 24-months resulting in complete remission of proteinuria and hematuria.

Case Description: The patient was referred to nephrology for evaluation of hematuria and proteinuria (1.5 g/g, Serum creatinine 0.9 mg/dl). Serological work-up was negative. She was initiated on angiotensin receptor blocker (ARB) and underwent kidney biopsy which confirmed IgA Nephropathy. There were 8 glomeruli with 20-25% sclerosis, mild to moderate chronic tubulointerstitial nephritis and fibrosis, no crescents, mild mesangial proliferation and hypercellularity with IgA staining 3+. She did not have any significant improvement in proteinuria despite maximally tolerated ARB (losartan 100 mg daily) therapy for three months. Her kidney function also declined, creatinine 1.2 mg/dl. Hydroxychloroquine 200 mg daily was then initiated along with regular eye exams and hepatic function tests. Repeat workup in three months showed improvement in proteinuria to 0.2 g/g and creatinine 1.1 mg/dl. She was continued on the same regimen for about 24-months with recent work-up showing complete resolution of proteinuria and hematuria.

Discussion: As per our literature review, this is the first reported case of IgA nephropathy treated with RAS inhibition and hydroxychloroquine over a span of almost two years resulting in complete remission. Hydroxychloroquine can be considered, in select cases, as an alternative to steroid therapy in refractory proteinuria.

Trend of serum creatinine and spot proteinuria measurement

PO1641

An International Delphi Survey on IgA Nephropathy: Results from the DEFINE Physicians Study

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Background: It is unclear whether treatment guidelines for patients with IgA nephropathy (IgAN) are uniformly applied in clinical practice. The DEFINE: Physicians initiative sought to describe the opinions of nephrologists about the pathophysiology, diagnosis, and optimal management of adult and pediatric patients with IgAN.

Methods: A 2-round Delphi survey was distributed to nephrologists in Canada, France, Germany, Italy, Spain, the UK, and the US. A 1-9 Likert scale (9=strongly agree) was used to score statements. Consensus was defined as median and mean score ≥75% of participants scoring agreement (ie, score 7-9). Feedback collected in Round 1 was used to revise statements not achieving high consensus (≤80% agreement) for retesting in Round 2. Moderate consensus was defined as 75-89% agreement.

Results: In Round 1, 207 participants with a median clinical experience of 18 years (range, 5-49) rated 19 statements about IgAN. Half (50%) of participants worked in nonacademic settings. All statements met criteria for moderate or high consensus after the second round. Notably, a statement on corticosteroid therapy in adult patients reached moderate consensus after Round 1 and was divided into 2 parts in Round 2 (Figure 1). Both revised statements reached levels of agreement similar to the original statement. In contrast, a statement on corticosteroid and cyclophosphamide use in adults with rapidly progressive glomerulonephritis and 2 statements on corticosteroid therapy in pediatric patients reached high consensus in Round 1 (Figure 1).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: High consensus regarding clinical decisions and the importance of controlling proteinuria in IgAN was observed in this Delphi survey. Although the level of consensus related to corticosteroid use was lower for adult patients vs pediatric patients, the level of consensus was relatively high for both groups.

Funding: Commercial Support - Traverse Therapeutics, Inc.

Methods: DEFINE: Physicians was a 2-round Delphi survey that recruited nephrologists from North America and Europe. A total of 22 FSGS/INS statements were scored using a 1-9 Likert scale (9=strongly agree). Consensus was defined as median and mean score ≥7, and ≥75% of participants scoring agreement (ie, score 7-9). Statements not achieving high consensus (≥80% agreement) in Round 1 were revised and restated in Round 2.

Results: This study involved 207 adult and pediatric nephrologists. Median clinical experience was 18 (range 5-49) years; 103 participants (50%) worked in nonacademic settings. In Round 1, 21 statements met consensus criteria and 7 statements not achieving high consensus were revised or divided into multiple parts, creating 11 revised statements for testing in Round 2. In Round 2, 9 of 11 statements met at least moderate consensus. Round 1 statements with high consensus described prognostic significance of proteinuria and disease management (Figure 1). Controversial statements restated in Round 2 pertained to distinction between primary and secondary FSGS in adults, and to management of frequently relapsing INS in children (Figure 2).

Conclusions: The level of consensus in this Delphi survey was high for statements on treatment decisions and the importance of proteinuria control. The main area where high consensus was not reached pertained to differentiation between primary and secondary FSGS and managing frequently relapsing INS in children, suggesting that these areas require further research.

Funding: Commercial Support - Traverse Therapeutics, Inc.

PO1642

Long-Term Effectiveness of Low-Dose Prednisone Treatment in Relapses of Steroid-Sensitive Minimal Change Disease

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Background: Treatment of relapses of steroid-sensitive minimal change disease (SMCD) involves administration of high doses of prednisone for several weeks, implying significant pharmacological toxicity. In a previous pilot study, the efficacy of treatment with low doses of prednisone for the treatment of relapses in these patients was demonstrated.

Methods: Retrospective analysis of SMCD relapses treated with low doses of prednisone in two centers, was performed, and the response to treatment, the time to reach remission and the free-time of relapse was studied, comparing it with previous relapses of the same patients treated with standard doses of steroids.

Results: 85 relapses in 21 patients with SMCD were analyzed. The median age of patients was 35 years (IQR 18-53), with 62% being male. The mean proteinuria at relapse debut was 5.37 ± 4.11 g/g, serum albumin 2.47 ± 0.94 gr/dL and creatinine 0.86 ± 0.35 mg/dL. Thirty-six relapses (42.3%) were treated with low doses of prednisone (LDP) and compared with 49 previous relapses (57.6%) of the same patients, treated with high doses of prednisone (HDP). The mean initial prednisone dose in relapses treated with LDP and HDP was 0.45 ± 0.1 mg/kg and 1.00 ± 0.3 mg/kg, respectively (p<0.001). The mean cumulative dose of prednisone in relapses treated with LDP and HDP was 1771 ± 1303 mg and 3894 ± 2134 mg respectively (p < 0.001). There were no differences in treatment duration between relapses treated with low and high corticosteroids doses (124 days vs 153 respectively; p=0.2). All patients achieved complete remission after steroid treatment. Mean time to remission was 18.4 days for relapses with LDP and 17.1 days for HDP (p = 0.6). The mean free time to relapse after treatment with low doses was 12.6 months vs 10.9 months for those treated with high doses (p = 0.6).

Conclusions: Among SMCD patients, treatment of relapses with low doses of prednisone (0.5 mg/kg) is effective and safe, allowing to minimize cumulative steroid doses and derived toxicity.

PO1643

DEFINE Physicians: An International Delphi Survey to Identify Consensus in the Care of Patients with FSGS or Idiopathic Nephrotic Syndrome

Marina Vivarelli,1 Keisha L. Gibson,2 Debbie S. Gipsen,2 Manuel Praga,4 Heather N. Reich,3 Michiel F. Schreuder,1 Vladimir Tesar,5 Marcello Tonelli,6 Jack F. Wetzels,7 Jai Radhakrishnan,8 Shirshak Aslam,2 John F. Neylan,2 Dana Rizk,3 Howard Trachtman,4 1Columbia University Irving Medical Center, New York, NY; 2Angion Biomedica Corp, Uniondale, NY; 3University of Alabama at Birmingham, Birmingham, AL; 4NYU Grossman School of Medicine, New York, NY.

Background: Primary nephritic syndrome (PPKDs) are among the leading causes of End-Stage Kidney Disease (ESKD). Receptor tyrosine kinases like PDGFR, DDR1, DDR2 are thought to play a role in the progression of PPKDs to ESKD. ANG-3070, a selective oral tyrosine kinase inhibitor, has demonstrated beneficial effects in chronic kidney disease animal models. Objective: Describe the design of a proof-of-concept study of ANG-3070 in the treatment of PPKD patients with persistent proteinuria while on standard of care (SOC).

Methods: A 12-week, randomized, double-blind, placebo-controlled study enrolling 100 patients with biopsy-proven PPKD and persistent proteinuria, ≥ 1 g/day, while on the SOC including maximum tolerated RAAS inhibitors. Patients will be randomized 1:1:1:1 to 200 mg or 400 mg once-daily or 300 mg twice-daily of ANG-3070 or placebo (Fig. 1). Results: The primary endpoint is the percentage change in 24-hr urinary protein at Week 12. Key secondary endpoints evaluated at week 12 include percentage change in 24-hr urinary albumin, number of patients with complete remission in proteinuria (24-hr urinary protein < 300 mg), number of patients with partial remissions in proteinuria (24-hr urinary protein reduction of ≥ 50% from the baseline and a 24-hr urinary protein < 3.5 g/day if the baseline 24-hr urinary protein > 3.5 g), number of patients with ≥ 50% reduction in 24-hr urinary protein from the baseline, and number of patients with a ≥ 50% reduction in 24-hr urinary albumin from baseline. An independent data monitoring committee will review safety throughout the study.

Conclusions: This Phase 2 study will provide data about the safety and efficacy of ANG-3070 in PPKD patients that will inform the design of a Phase 3 study.

Funding: Commercial Support - Angion Biomedica, Inc.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

512
PO1645
Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) for the Treatment of Pediatric Nephrotic Syndrome (NS)
Christine B. Sethna,1,2 Kumail Merchant,1 Stavros Zanos,2 Timir Datta-Chaudhuri,1 Pamela Singer,1 Laura J. Castellanos,3 Rachel Frank,1 Steven and Alexandra Cohen Children’s Medical Center, New Hyde Park, NY; 2Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.

Background: Children with NS, especially those with frequent relapses (FRNS) or steroid resistance (SRNS), are exposed to prolonged courses of immunosuppressant medications with side effects and variable efficacy. There is an urgent need to identify novel and safe therapies to treat pediatric NS. taVNS modulates the immune system via the cholinergic anti-inflammatory pathway and has become a therapy of interest for treating immune-mediated illnesses. The objective was to conduct an open-label early feasibility study of taVNS therapy for pediatric NS.

Methods: Children with FRNS (≥2 relapses in previous 6 months) or SRNS (no remission after 4 weeks of steroids) were enrolled. Participants with FRNS were in remission and off immunosuppression (off steroids >14 days and other immunosuppression >3 months). SRNS patients were on a stable regimen of medications for 6 months prior to enrollment. Participants performed taVNS therapy 5 minutes daily for 6 months with a TENs 7000 unit. taVNS was delivered to the auricular branch of the vagus nerve via the left cymba concha. Cytokine levels were compared using the Wilcoxon test.

Results: Seven participants (3 FRNS, 3 SRNS, 1 genetic congenital nephrotic syndrome [CNS]) had a median age of 7 years (range 3-17) and 63% were male. FRNS participants remained relapse-free during the study period (two continued taVNS at 9 and 13 months and remained in remission). SRNS participants had a 25-76% reduction in urine protein to creatinine ratio (upc) compared to baseline (Figure). Upe decreased (13.7%) in the participant with CNS but remained in nephrotic range. All but one participant (non-compliant) had a reduction in TNF-α (7.33pg/mL vs. 5.46pg/mL, p=0.03). No adverse effects were reported.

Conclusions: taVNS prevented NS relapses in FRNS, reduced proteinuria in SRNS, and reduced TNF-α levels without any adverse effects, suggesting taVNS as a promising therapy for pediatric NS. A larger, randomized clinical trial is needed to confirm these findings.

PO1646
A Study Comparing Rituximab and Modified Ponticelli (MP) Regimen in Primary Membranous Nephropathy (PMN)
Abhishek Kumar, Arpita Ray Chaudhury, Saugat D. Gupta, Sriranjan Mukherjee, Moumita Sengupta. IPGIMER Nephrology Institute of Postgraduate Medical Education and Research, Kolkata, India.

Background: The study was designed in December 2018 when the Gemritux trial had established Rituximab as an alternative to MP regimen in the treatment of PMN. So we designed a study comparing Rituximab and MP Regimen.

Methods: We allocated 35 adults with PMN and proteinuria >3.5 gm/day in a 3:2 ratio to MP regimen or Rituximab 375mg/m² on days 1,8,15 and 22. The primary outcome was complete or partial remission (CR+PR) at 6 and 12 months in the 2 groups. The other findings included trends of 24 hr urine protein, albumin, creatine and serious adverse events at 6 and 12 months in both groups.

Results: At 6 months, 12 of 21 patients (57.14%) allocated to MP Regimen and 5 of 14 patients (35.71%) allocated to Rituximab experienced remission (CR+PR) (odds ratio [OR], 2.4; 95% CI, 0.596−9.670, p value 0.10). At 12 months, 14 of 21 patients (66.66%) allocated to MP Regimen and 10 of 14 patients (71.43%) allocated to Rituximab experienced remission (CR+PR) (odds ratio [OR], 0.8; 95% CI, 0.184−3.487, p value 0.383). Serious adverse events occurred in 15% of patients receiving Rituximab and in 24% receiving the MP Regimen.

Conclusions: We found No Statistically Significant difference between Rituximab and the Modified Ponticelli Regimen in the treatment of membranous nephropathy. A head-to-head, longer follow up study comparing MP Regimen versus Rituximab is required in terms of duration of remission and side effect profile between the two treatment groups.

Funding: Government Support - Non-U.S.
Methods: M-PLACE (NCT04145440) is an open-label, multi-national Phase Ib/II study of adults with anti-PLA2R+ MN requiring immunosuppressive therapy (IST). Cohort 1 includes de novo and IST-relapsed pts (n=20) and Cohort 2 IST-refractory pts (n=10). Participants receive nine felzartamab infusions (16 mg/kg) over six 28-day cycles (weekly in Cycle 1; monthly thereafter), followed by a 26-week observational follow-up. Concomitant IST use is prohibited. The primary endpoint is the incidence and severity of treatment-emergent adverse events. The key secondary endpoint is the immunologic response rate, as determined by anti-PLA2R Ab reductions. Exploratory endpoints include evaluations of proteinuria and kidney function.

Results: As of April 2021, 12/30 planned pts were enrolled (Cohort 1, n=8; Cohort 2, n=4). Median age was 62.5 years (range 43 to 77 years), 83% were male, and median baseline anti-PLA2R Ab titer was 178 U/mL (18 to 1027 U/mL). Seven pts had received ≥4 weeks of felzartamab therapy. At Week 4, 5/7 pts had a ≥50% reduction from baseline in anti-PLA2R Ab (Cohort 1, n=3; Cohort 2, n=2); the other 2/7 pts had reductions from baseline of −16.8% to −5.0% (both Cohort 1). Mean % decline in anti-PLA2R Ab from baseline to Week 4 was −53.0% (−92.0% to −5.0%). B-cell counts were not markedly changed from baseline. Felzartamab was well tolerated.

Conclusions: The M-PLACE proof-of-concept study has so far shown that felzartamab rapidly and substantially reduces anti-PLA2R Ab titers in pts with anti-PLA2R+ MN. Longer follow-up is required to assess felzartamab safety and efficacy in this population.

Funding: Commercial Support - MorphoSys AG

PO1648
Evaluating the Efficacy of Rituximab in Primary Membranous Nephropathy: An Observational Study from Southern India
Megha Saigal, Swarnalatha Guditi. Nizam’s Institute of Medical Sciences, Hyderabad, India.

Background: Membranous nephropathy, is an immunological disease. It can occur secondary to infection, malignancy, or SLE. In 70% of patients M-type phospholipase A2 receptor (PLA2R) was positive, and these patients are considered to suffer from secondary immunosuppressive agent in primary MN has not been evaluated among Indian population.

Methods: Single centre observational pilot study 20 subjects with histological/serum PLA2R positive progressive primary membranous nephropathy were recruited. They were then either started on conventional immunosuppressive therapy (modified ponticelli regimen) and if no or partial response were initiated on rituximab as a second line agent or in some cases as a primary immunosuppressive agent. Rituximab was started at 375mg/m2 weekly doses. Data regarding urine protein creatinine, serum albumin, serum creatinine, CD 19 count, time to achieve to remission and side-effects were noted.

Results: In our study, males were 65% (13), females contribute to 35% (7). After 8 weeks, 71% of patients were in immunological remission. As of April 2021, 12/30 planned pts were enrolled (Cohort 1, n=8; Cohort 2, n=4). Median age was 62.5 years (range 43 to 77 years), 83% were male, and median baseline anti-PLA2R Ab titer was 178 U/mL (18 to 1027 U/mL). Seven pts had received ≥4 weeks of felzartamab therapy. At Week 4, 5/7 pts had a ≥50% reduction from baseline in anti-PLA2R Ab (Cohort 1, n=3; Cohort 2, n=2); the other 2/7 pts had reductions from baseline of −16.8% to −5.0% (both Cohort 1). Mean % decline in anti-PLA2R Ab from baseline to Week 4 was −53.0% (−92.0% to −5.0%). B-cell counts were not markedly changed from baseline. Felzartamab was well tolerated.

Conclusions: The M-PLACE proof-of-concept study has so far shown that felzartamab rapidly and substantially reduces anti-PLA2R Ab titers in pts with anti-PLA2R+ MN. Longer follow-up is required to assess felzartamab safety and efficacy in this population.

Funding: Commercial Support - MorphoSys AG

PO1649
Intravenous Cyclophosphamide vs. Calcineurin Inhibitors as Treatment in High-Risk Idiopathic Membranous Nephropathy: The Benefit in MAKE Is Preserved in the Presentation IV
Angela M. Cordoba Hurtado,1 L. M. Perez-Navarro,1 Jesus D. Lima-Lucero,1 Virgilia Soto,2 Rafael Valdez-Ortiz.1 Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico; Instituto Nacional de Cardiología Ignacio Chavez, Mexico, Mexico.

Background: The use of intravenous cyclophosphamide (IV CYC) in high-risk idiopathic membranous nephropathy (IMN) has not been fully evaluated in the make primary endpoints (serum Cr doubling, ERSD, mortality). In our center, the treatment of high-risk IMN is performed with IV CYC or with calcineurin inhibitors (CNI) according to criteria of accessibility and availability of the drug. Our aim was to compare the immunosuppressive treatment scheme with IV CYC vs CNI in primary MAKE events in patients with high-risk IMN.

Methods: Retrospective cohort study. Patients with a diagnosis of IMN diagnosed between January 2012 and January 2020 were included. The patients were treated with IV CYC or CNI. With a minimum follow-up of 12 months and MAKE primary events were recorded in addition to complete, partial, composite response and adverse events at the end of the study.

Results: Thirty-seven patients of which 14 (37.8%) were treated with IV CYC and 23 (62.2%) with CNI. The mean age was 46 ± 15.3 years, 54% male, and 27% hypertensive. Average Pts/ Cr/ CrTU 10.43 ± 4.4 gr/g; mean serum albumin 1.8 ± 0.68 g/dL; and GFR by CKD EPI of 75min/mL/1.73m2. With a follow-up of 45.91 ± 23.9 months, no baseline differences were observed between the groups. Table 1 shows the comparison between IV CYC vs CNI for high-risk IMN shows similar outcomes focused on MAKE. However, the comparison in composite and partial response shows a result in favor of the use of CNI. This perspective provides clinical evidence about the use of IV CYC, which is why it is suggested that there are possible differences between our findings and those reported so far with oral CYC. Prospective clinical trials are required to have conclusive results.

Table 1. outcomes by treatment IV CYC vs ICN

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV CYC</th>
<th>ICN</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Complete response</td>
<td>28.6</td>
<td>56.0</td>
<td>0.54</td>
</tr>
<tr>
<td>Partial response</td>
<td>7.12</td>
<td>30.4</td>
<td>0.011</td>
</tr>
<tr>
<td>Compound remission</td>
<td>35.7</td>
<td>85.9</td>
<td>0.008</td>
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<tr>
<td>Relapses</td>
<td>20.8</td>
<td>25</td>
<td>0.82</td>
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<tr>
<td>MAKE</td>
<td>15.5</td>
<td>18</td>
<td>0.8</td>
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PO1650
An 8-Week Course of Cyclophosphamide and Steroids Is Effective Therapy in Patients with Membranous Nephropathy (MN) and Low PLA2R Levels
Coralin Vink- van Setten,1 Anne-Elis van de Logt,1 Alexander Kühnl,2 Jack F. Wetzel,3 1Radboudumc, Nijmegen, Netherlands; 2EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany.

Background: We introduced individualized therapy in patients with MN and positive anti PLA2R antibodies (aPLA2R) by IFIst test. Treatment (cyclophosphamide combined with steroids) was stopped when the IFT test (measured at 8, 16, or 24 weeks) became negative. After 8 weeks, 71% of patients were in immunological remission. Unfortunately, 30% of these latter patients needed renewed therapy within 12 months because of immunological and/or clinical relapse. We questioned if quantitative aPLA2R measurement would predict response.

Methods: Available, stored serum samples were retrieved, and aPLA2R levels were measured by ELISA (EUROIMMUN Lübeck, Germany). Good outcome was defined as immunological remission at 8 weeks, followed by clinical remission without clinical relapse or the need for additional immunosuppressive therapy within 12 months.

Results: Serum samples of 60 patients were available for analysis. Patients were grouped according tertiles of aPLA2R (Table). Higher aPLA2R levels were associated with more severe proteinuria. Patients in the lowest tertile were more likely to develop immunological remission at 8 weeks (95% vs 65% and 50% in the middle and highest tertiles). Moreover, in the subgroup of patients who were treated for 8 weeks only, fewer patients in the lowest tertile of aPLA2R needed renewed immunosuppressive therapy, although not statistically significant (16% vs 43%, p = 0.05).

Conclusions: Individualized treatment of MN patients with cyclophosphamide and steroids has been recently introduced. In this study we show that baseline aPLA2R levels predict immunological remission at 8 weeks. Furthermore, patients with low aPLA2R at baseline seem to be more likely to have a good overall outcome.

Funding: Commercial Support - EUROIMMUN research lab, Lübeck, Germany
Baseline clinical characteristics and immunological remission at week 8

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (yrs)</th>
<th>Male/female</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Proteinuria (g/day)</th>
<th>Urinary Albumin (mg/gCr)</th>
<th>Total IgG (g/L)</th>
<th>Total IgM (g/L)</th>
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<td>12</td>
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<td>20-60</td>
<td>12</td>
<td>70</td>
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</table>

Data shown as mean±SD or median[IQR]. *By Kruskal–Wallis test of Fishers’ exact test, as applicable

PO1651
Prospective Cohort Study of Antibody-Guided Therapy in Patients with Membranous Nephropathy

Background: Guidelines advise a standard course of 6 months of cyclophosphamide (CP) and steroids in patients with membranous nephropathy (MN). We hypothesized that monitoring of aPLA2R-antibodies (aPLA2R) may enable individualized (and shorter duration of) therapy.

Methods: Patients with MN, with positive aPLA2R and high risk of progression were included. Treatment consisted of CP (1.5 mg/kg/day combined with steroids). aPLA2R were monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If the IFT test was negative, CP was stopped and prednisone tapered. If the IFT test remained positive at 24 weeks, CP was switched to MMF and therapy continued.

Results: Sixty-five patients (48 males) were included; mean age 61 ± 12 yrs, median serum creatinine 156 [IQR 100-161] µmol/l, serum albumin 21 [IQR 16-26] g/l and UPCR 7.7 [IQR 5.4-11.1] g/10 mmol. Follow-up was 37 [IQR 27-58] months. aPLA2R test was negative in 46 patients after 8 weeks (group A), in 10 patients after 16 weeks (group B1), in 1 patient after 24 weeks (group B2) and in 8 patients aPLA2R remained positive after more than 24 weeks (group B3). In group A no clinical remission (PCR <3.0 g/10 mmol) was observed in 26 % (12 patients) compared to 21 % (4 patients) in group B1-B3 (Log rank p=0.579). Overall 22 patients (34 %) received additional immunosuppressive (IS) therapy because of persistent proteinuria (after aPLA2R disappearance) or clinical relapse. IS free survival was lower in group A compared to group B1-B3. (Figure 1).

Conclusions: Approximately 50% of patients developed long-term clinical remission after 8 weeks of therapy. Our data support aPLA2R-guided therapy. However, in approximately 25% of patients immunological remission was not followed by clinical remission, underlining the need for better biomarkers.

Funding: Other NIH Support - Dutch Kidney Foundation

PO1652
Economic Evaluation of the MENTOR Trial Comparing Rituximab and Cyclosporine for the Treatment of Membranous Nephropathy (MN)
Matthew J. Kadatz,1,2 Scott Klarenbach,1 Helen So,1 Fernando C. Fervenza,3 Daniel C. Cattran,1 Sean Barbour.1 On behalf of the MENTOR trial investigators 1The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; 2Vancouver Coastal Health Research Institute, Vancouver, BC, Canada; 3University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; 4Mayo Clinic Minnesota, Rochester, MN; 5University of Toronto, Toronto, ON, Canada.

Background: The MENTOR trial (Membranous Nephropathy Trial Of Rituximab) showed that rituximab (RTX) was noninferior to cyclosporine (CSA) in inducing complete or partial remission of proteinuria and was superior in maintaining proteinuria remission. However, the cost of RTX is high and it’s cost-effectiveness has not been determined.

Methods: A Markov model (Fig 1) was used to determine the incremental cost-effectiveness ratio (ICER) of RTX compared with CSA for the treatment MN from the perspective of a health care payer with a life-time time horizon ($2020 USD). The model outcomes were informed by data from the MENTOR trial and previously published literature. Cost and utility inputs were obtained from the literature.

Results: Based on 1,000 simulations, the mean additional cost of RTX therapy for MN compared with CSA was $168,064 with an improvement in utility of 6.70 QALYs (Fig 2). RTX was cost-effective (assuming a willingness-to-pay threshold of $50,000 / QALY) compared with cyclosporine, with an ICER of $25,071 per additional quality adjusted life year (QALY) over a lifetime time horizon (45 years).

Conclusions: While the initial cost of RTX is high, RTX is a cost-effective option (assuming willingness to pay thresholds of $50,000 or greater) for the treatment of MN when compared with the alternative of CSA. The cost-effectiveness will be further improved with the use of less expensive biosimilars.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO1653
A Multicenter, Prospective, Open-Labeled Study of Acthar Gel Alone or with Tacrolimus to Reduce Urinary Proteinuria in Patients with Idiopathic DNA-JB9-Positive Fibrillary Glomerulopathy
James A. Tumlin,1 Richard A. Lafayette,2 Andrew S. Bomback,2 Amber S. Podoll,4 FACT Trial Group 1Emory University, Atlanta, GA; 2Columbia University, New York, NY; 3Stanford University, Stanford, CA; 4University of Colorado - Anschutz Medical Campus, Aurora, CO.

Background: Fibrillary Glomerulopathy (FGN) is a rare primary glomerular disease characterized by glomerular accumulation of nonbranching, randomly arranged 10-30 nm in diameter fibrils. The resulting podocyte dysfunction and progressive proteinuria leads to ESRD rates of 50% within 4 years. Herein we present data on 15 patients treated with ACTH or ACTH + Tacrolimus completing 12 months of therapy.

Methods: Study Design: Randomized prospective open labeled study of 12 months of SQ ACTH alone or with Tacrolimus completing 12 months of therapy.

Results: Of the 15 patients completing 12 months of treatment, 14.3% achieved complete remission (UP/Cr ratio < 300 mg/gm); 26.0% achieved a ≥ 75% reduction from baseline, while 60.7% achieved a ≥ 50% reduction in UP/Cr at 12 months. A total...
of 86.6% achieved a minimum 30% reduction in U/P Cr. The addition of Tacrolimus to ACTH tended to further lower U/P Cr at 12 months (1654.7±317 vs. 4449.5±1665) respectively, but did not reach statistical significance.

**Conclusions:** In summary, de-ropository ACTH induced a complete or partial remission in 75% of patients with DNA-JH9 + Fibrillary GN. The addition of Tacrolimus in this population tended to improve complete-partial response rates.

**Funding:** Commercial Support - Mallinckrodt Pharmaceuticals, Clinical Revenue Support

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**PO1655**

**Early Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome Is Safe and Cost-Effective**


**Background:** The introduction of eculizumab has improved outcome in patients with atypical hemolytic uremic syndrome (aHUS). The optimal treatment strategy is debated. It is unknown if unbiased withdrawal of eculizumab is a safe strategy. Here we report the results of the CUREiHUS study, a national observational study monitoring eculizumab discontinuation in Dutch aHUS patients after three months of therapy.

**Methods:** All pediatric and adult aHUS patients with native kidneys and first-time eculizumab treatment (n=21) were evaluated. At last follow-up, there were no chronic sequelae, i.e. no clinically relevant increase in serum creatinine, proteinuria and/or hypertension, in the relapsing patients. No clinically relevant predictors of relapse (including the presence of a pathogenic mutation) could be determined. The total medical expenses, including costs of among others others hospital admission and disease recurrence, of our population were only 33% of the fictive expenses made when patients would have received eculizumab every fortnight.

**Conclusions:** It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS in native kidneys. Larger data registries are needed to determine factors to predict relapse(s) and short- and long-term outcomes.

**PO1656**

**Outcome of Kidney Transplantation in Atypical Hemolytic Uremic Syndrome Without Eculizumab Prophylaxis: A Single-Center Experience**

Caroline Duineveld, Romy N. Bouwmeester, Kiao L. Wijnmsa, Nicole Van De Kar, Jack F. Wetzels. Radboudumc, Nijmegen, Netherlands.

**Background:** A high risk of aHUS recurrence (60-80%) is reported after kidney transplantation. Therefore, it is suggested to perform kidney transplantation in aHUS patients with eculizumab prophylaxis. In 2017 we reported a favorable outcome after kidney transplantation in aHUS patients without eculizumab prophylaxis, using kidneys from living donors and a transplantation protocol aimed at reduction of endothelial injury. It is unknown if unbiased withdrawal of eculizumab is a safe strategy. Here we report the results of our treatment protocol with prolonged follow-up.

**Methods:** All patients with a previous history of aHUS who received a living or deceased donor kidney transplantation in the Radboud University medical center between 2011 and 2020 were evaluated.

**Results:** We included 26 aHUS patients (M 9; F 17, median age at transplantation 47y, range 22-69). In 22 patients (85%) 24 genetic variants were found: C3 (N=14), CFH (N=8), CFB (N=2). Recurrence risk was considered high in 18 patients and moderate in 8 patients. Nineteen patients received a graft from a living donor (LD) and 7 patients a graft from a brain-death deceased donor (DBD). All patients were treated with low-dose tacrolimus. Six patients (23%) developed aHUS recurrence (4/19 LD, 2/7 DBD) and were treated with eculizumab. Of note, recurrence occurred >12 months after transplantation in two patients. No patient lost the graft due to aHUS recurrence. One patient lost the graft due to rejection and BK nephropathy, one patient died with a functioning graft due to infections. After a median follow-up of 63.6 months (range 12-116) median eGFR was 53.5 ml/min/1.73m2, and proteinuria was negligible (median urine protein-creatinine ratio 0.12 g/100mmol, range 0.04-0.6).

**Conclusions:** It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS in native kidneys. Larger data registries are needed to determine factors to predict relapse(s) and short- and long-term outcomes.
PO1657
Podocytes Soften in Proteinuric CKD: A Potential New Mechanism for Proteinuria?

Luisa Ulloa severtón,1 Xiaolin He,2 Franziska Lausecker,2 Rachel Lennon,2 Mira Kendzé,2 Darren A. Yuen,2 Yuen Lab ’St Michael’s Hospital, Toronto, ON; 2Department of the University of Manchester Faculty of Biology Medicine and Health, Manchester, United Kingdom; 1State University of New York Upstate Medical University, Syracuse, NY.

Background: Proteinuria is one of the most common manifestations of glomerular injury, and an important predictor of disease progression. Podocytes are a critical component of the glomerular filtration barrier, and as such podocyte injury is a major cause of proteinuria. Historically, investigators have focused on biochemical changes in podocytes that occur following podocyte injury. In contrast, little is known about the changes in the physical properties of these high-scaled epithelial cells.

Methods: 3 different models of proteinuric glomerular disease were studied: (1) Akita-/- Ren-/- mice (a murine model of diabetes and renin-mediated hypertension that we have recently shown develops progressive glomerulocarcinosis that mimics human diabetic kidney disease, n = 7); (2) Myo1e-/- mice (a mouse model of genetic FSGS characterized by deficiency of a non-muscle myosin involved in actomyosin contraction, n = 6); and (3) Col4a5-/- mice, a mouse model of Alport’s syndrome (n = 12). The stiffness of glomeruli, glomerular basement membrane (GBM), and podocytes was measured using atomic force microscopy (AFM) and associated histology (picrosirius red, silver, and WT1 staining). Similar stiffness measurements were performed in human FSGS and healthy kidney donor biopsies.

Results: AFM measurements revealed that glomerular stiffness increased in Akita-/- Ren-/- and Col4a5-/- mice, a finding that correlated with the degree of glomerulosclerosis. Glomerular stiffness was not increased in Myo1e-/- mice. GBM stiffness was increased in Akita-/- Ren-/- and Myo1e-/- mice, but not in Col4a5-/- Alport’s mice. In all 3 mouse models, as well as in human FSGS biopsies, podocytes were softer than in healthy control kidneys.

Conclusions: Taken together, these are the first data demonstrating that podocytes soften in proteinuric glomerular disease. Given the major rearrangements in the actomyosin network that occur in podocytes of proteinuric kidneys, our data suggest that podocyte injury, and an important predictor of disease progression, Podocytes are a critical component of the glomerular filtration barrier, and as such podocyte injury is a major cause of proteinuria. Historically, investigators have focused on biochemical changes in podocytes that occur following podocyte injury. In contrast, little is known about the changes in the physical properties of these high-scaled epithelial cells.

PO1658
Novel Small Molecule Compounds Protect Podocytes from Injury In Vitro and In Vivo

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Background: Podocyte dysfunction and loss is a key determinant of proteinuria and glomerular injury. Thus, maintaining healthy podocytes is a therapeutic strategy against kidney disease. We previously developed a high-content imaging-based assay and used it to screen a number of small molecule compounds that show protection of podocytes from injury, suggesting it to be a viable strategy for the discovery and development of novel podocyte-protective agents.

Methods: Differentiated mouse podocytes were seeded on collagen-I coated multi-well plates as previously described (Lee et al. JASN, 2015). Cells were exposed to puromycin aminonucleoside (PAN, podocyte injury inducing agent), with compounds from the screening libraries, or DMSO as control, for 48 hours. Cells were fixed and stained which allowed detection using the Opera High-Content Screening (HCS) System. Columbus software was used to quantify morphology properties such as rounding, as well as the overall F-actin signal. Drosophila based screening assays were used to determine efficacy of selected hits in vivo.

Results: PAN damage resulted in quantitative reduction in F-actin fiber numbers and intensity, and increased rounding in podocytes in the ultra-miniaturized assay system. Screening of a library of chemical compounds identified >28 hits that dose-dependently reduced podocyte damage. A set of 9 compounds showed significant protection in a drosophila model of kidney injury, supporting the findings from the high-throughput screening assay.

Conclusions: Our 1536-well plate-based assay system identified a number of small molecule compounds that dose dependently protected podocytes from damage in vitro. A drosophila model of kidney injury validated most of the in vitro data from the podocyte screening assay in vitro and in vivo mechanistic studies are underway to elucidate new insights into podocyte pathways that are therapeutically targeted by the selected hits. These agents hold promise as novel therapeutics for kidney disease patients with podocyte pathologies.

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PO1659
Characterization of the Direct Effect of Mycophenolic Acid on Murine Podocytes

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Background: Mycophenolic Acid (MPA) is the active component of Mycophenolate Mofetil, a selective, noncompetitive inhibitor of the inosine monophosphate dehydrogenase. Blockade of the de novo purine synthesis depletes the pool of deoxyguanosine triphosphate, leading to a specific suppression of proliferation of B- and T-Lymphocytes. MFA has an established role as a therapeutic agent in childhood nephrotic syndrome, where it currently serves as a second line option for frequent relapsing and steroid dependent cases. Although its immunological functions are well studied, direct effects of MPA on podocytes remain largely unknown. With first preliminary results showing a protective effect in vivo, the present study aims to examine the direct effect of MPA on murine podocytes and its abilities to alter albumin-induced podocyte injury.

Methods: Cultured murine podocytes were exposed to albumin for 48 hours, with one group receiving treatment with MPA for the second 24 hours. Cells were stained with a Synaptopodin antibody and additional markers to visualize components of the cytoskeleton. Currently, we are analyzing apoptosis through a TUNEL assay as well as alterations in intracellular Calcium content with Fluo-4 and fura red. In addition, we study podocyte stiffness under injury with MPA intervention and use real-time fluorescence. We will also study small GTPases content and activity through a pull-down assay for RhoA and Rac1. In an unbiased approach, podocytes were exposed to either 2 hours of 10 mg/1 MP A or an additional 22 hours of 4 mg/1 MPA. Total RNA was isolated and subjected to RNAseq analyses.

Results: Synaptopodin immunofluorescence shows significant alterations of the actin cytoskeleton through albumin exposure. MPA treated cells reveal a restorative ability of the drug, with a recovery of stress fiber formation and a reduction of albumin-induced vacuoles. mRNA expression data from the RNAseq analysis will provide an objective and detailed picture of the direct effects of MPA on podocytes.

PO1660
Integration of Plasma Proteomics and Metabolomics Revealed Multiple Protein-Metabolite Networks in Steroid-Resistant Nephrotic Pediatric Patients

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Background: Nephrotic Syndrome (NS) is a common glomerular disease in children. Childhood NS (NSC) and steroid-dependent NS (SSNS) are the mainstays, whereas the NS with steroid-resistant NS (SRNS) develops in 5-20% of children, dramatically increasing risk for progressive CKD vs. children with steroid sensitive NS (SSNS). There are no validated biomarkers able to predict which children will have SRNS. Here, we used previously published plasma proteomic and metabolomic profiles from children with SSNS and SRNS to test the hypothesis that integrating proteomic + metabolomic data could identify biomarkers and/or targets to define SRNS pathways that were not identified in the individual datasets.

Methods: Proteomic data from 15 paired NS plasma samples (n=7 SSNS; n=8 SRNS) and metabolomic data from the same subjects underwent joint pathway analyses using Metabo Analyst 5.0 software. Fold change (FC) was calculated as the ratio of pre-treatment to post-treatment for each protein and metabolite, and then log2 transformed. Proteins with LogFC>10 or LogFC<-10 and metabolites with Log FC<1 or Log FC>1 were included in the analyses.

Results: Pathway analyses of proteomic data identified “ECM receptor interaction” and “focal adhesion” as the most significantly up- and down-regulated pathways in SRNS vs. SSNS, whereas “Valine, Leucine & Isoleucine biosynthesis”, and “Glycosaminoglycan biosynthesis” were the most up- and down-regulated metabolic pathways in SRNS, respectively. The integrated proteomic + metabolomic pathway map identified 3 metabolic pathways that were perturbed in SRNS but not in SSNS: 1) “Nicotinate & Nicotinamide” pathway was perturbed in 50% of SRNS subjects (4 SRNS vs. 0 SSNS), 2) “Butanoate” pathway was perturbed in 37.5% of SRNS subjects (3 vs. 0), and 3) “Glycine, Serine & Threonine” metabolism was perturbed in 25% of SRNS subjects (2 vs. 0).

Conclusions: Integrating proteomic + metabolomic data from children with SRNS vs. SSNS have identified multiple pathways and protein-metabolite linkages with potential to become future candidate biomarkers or drug targets of SRNS.
PO1661
Spatially Resolved Analysis of Glomerular Structures in Alport Syndrome and FSGS

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Background: Many transcriptomics studies highlighted the molecular mechanism underlying glomerular disease, but very little is known about interglomerular heterogeneity and how each glomerulus is affected during progressive CKD. Using Spatial transcriptomics, which allows the characterization of the gene expression based on morphological context, we showed important differences between glomeruli of Alport Syndrome (AS) and FSGS patients and defined the interactive gene networks involved in glomerulus damage using healthy glomeruli as reference.

Methods: Using the Nanostring GeoMX Spatial Differential Profiling (DSP, Whole Transcriptomic Atlas) we generated spatial maps of gene expression of human AS (COL4A5 and COL4A6) and FSGS glomeruli (both males and females) and compared them to age-matched healthy controls. A total of 90 regions of interest were selected. After data QC and normalization, data were analyzed using different platforms and integrated with histopathology assessment.

Results: Data distinguished genes associated with podocyte, glomerular endothelial and mesangial cell phenotype. Unsupervised clustering and dimensionality reduction analysis showed clear differences between not only diseased and normal glomeruli (which presented homogenous gene expression profile), but also between glomeruli of AS vs FSGS. Though glomeruli of AS and FSGS were histologically similar within each sample, they presented different transcriptomic profiles (for instance, while oxidative phosphorylation, focal adhesions were common to all gloms in AS, Apelin, PI3K-Akt and Hippo signaling were unique to only a few glomeruli). Marked differences between males and females were observed in both AS and FSGS glomeruli (sheer stress and leukocyte transendothelial migration was more typical in AS male than female, while insulin signaling was only present in AS female). Similar heterogeneity patterns were observed in FSGSs. In contrast to FSGS, AS were more enriched for genes associated with TCA cycle, protein processing in the ER, and neurotrophin signaling.

Conclusions: DSP revealed significant interglomerular heterogeneity in AS and FSGS regardless of age and gender leading to the discovery of pathways defining disease phenotypes at single glomerulus level. These preliminary data using DSP may allow the discovery of potential new therapeutic targets for CKD patients.

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PO1662
EGR1 Is an Injury Marker in Podocytes

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Background: There is no good marker that depicts injured podocytes in human histology samples as well as desmin staining in rodent samples. EGR1 (Early Growth Response 1) is an injury marker in podocytes in human glomeruli. This study aimed to explore an association between EGR1 staining in podocytes and podocyte injury in human glomerular diseases.

Methods: Patients who underwent kidney biopsy at Jikei University Hospital, Tokyo, from June 2018 to March 2020 were recruited. Exclusion criteria included age ≤20 years, glomeruli < 8 tubulointerstitial diseases, and kidney transplant patients. Blood and urine were collected during the kidney biopsy, and estimated glomerular filtration rate (eGFR), urinary protein to creatinine ratio (UPCR), urinary nephrin mRNA, and urinary podocin mRNA were analyzed. For the kidney biopsy specimen, the percentage of glomeruli with podocytes expressing EGR1 (%EGR1), the percentage of sclerotic glomeruli (%GS), and the glomerular podocin expression scores were measured. The %EGR1 was compared with these parameters using Spearman’s rank correlation coefficient.

Results: Ninety-eight patients were included in this study (male, 58%; median age, 49 [interquartile range, 36–60] years; eGFR, 65 [44–79] mL/min/1.73 m², UPCR, 0.90 [0.43–2.46] g/g; %EGR1, 26.1 [14.6–41.4%]; IgA nephropathy, n=35; hypertensive nephrosclerosis, n=10; membranous nephropathy, n=6; lupus nephropathy, n=5; minimal change disease (MCD), n=2; focal segmental glomerulosclerosis (FSGS), n=9; %GS was correlated with UPCR, urinary nephrin mRNA, urinary podocin mRNA, and glomerular podocin expression scores (r=0.303, 0.378, 0.369, and -0.286; and P=0.0024, <0.001, 0.001, and 0.0043, respectively) but not with eGFR and %GS. In the absence of nephropathy, %EGR1 was also correlated with UPCR and urinary podocin mRNA (r=0.413 and 0.378; and P=0.014 and 0.025, respectively). Interestingly, the %EGR1 was low in MCD (8.33 [0.0–15.4%]), and high in FSGS (40.0 [36.8–46.3%]).

Conclusions: EGR1 expression in podocytes is associated with podocyte injury. EGR1 could be a podocyte injury marker in human glomeruli.

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PO1663
The CLVS1 H310Y Variant Associated with Steroid-Responsive Nephrotic Syndrome Affects Podocyte Function and Glomerular Filtration Barrier Integrity

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Background: We identified a rare homozygous variant, p.H310Y, in the gene encoding clavesin1 (CLVS1) as a novel cause of steroid sensitive nephrotic syndrome (SSNS) in a backcross-down of the c.1579G>A (p.H526R) mutation detected in edema phenotypes that could be rescued with WT CLVS1 mRNA but not the H310Y variant. CLVS1 knockout in cultured human podocytes decreased endocytosis, increased reactive oxygen species (ROS) accumulation, and increased apoptosis. These aberrant phenotypes were rescued in the presence of glucocorticoids, mimicking the steroid responsive phenotype of CLVS1 H510Y patients.

Methods: To better understand the effects of the CLVS1 H510Y variant on podocyte homeostasis, we created human podocyte cell lines with CRISPR-Cas9 mediated heterozygous and homozygous CLVS1 H310Y knock-in (KI) mutations. We evaluated the KO and KI podocytes through automated live-cell imaging. Additionally, we further evaluated the effects of reduced CLVS1 function on podocyte function in vivo in zebrafish. Wild-type and mutant clavesin1 is expressed ubiquitously in zebrafish larval kidneys. CLVS1 knockout in cultured human podocytes. Additionally, transgenic H310Y KI KO displayed similar corticosteroid responsive phenotypes to CLVS1 KO lines, including increased apoptosis that could be rescued with ROS inhibition, while heterozygous KI lines were unaffected. Furthermore, we confirmed that the H310Y variant reduces binding to a critical antioxidant transporter, alpha tocopherol transfer protein (p=0.006), likely contributing to the ROS phenotypes. Electron microscopy analysis and quantification of excreted proteins revealed podocyte effacement and decreased glomerular filtration barrier integrity in zebrafish with knockdown of orthologous CLVS1 when compared to controls (p<0.0001).

Conclusions: Our data further demonstrates the importance of clavesin1 in the maintenance of podocyte viability and GFB integrity. It also suggests that oxidative stress regulation may be compromised in patients carrying pathogenic CLVS1 variants and highlights the potential for alternative therapies for NS patients that target ROS accumulation in podocytes.

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PO1664
Rare Variants in RCAN1-3 Genes Are Enriched in Patients with CKD

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Background: We recently identified rare variants in the gene encoding Regulator of Calcineurin Type 1 (RCAN1) as a novel cause of FSGS/SRNS. Cells expressing mutant RCAN1 and human podocytes with reduced RCAN1 displayed increased CN activity (p=0.4946, 0.3980 and 0.0912 respectively) and reduced viability (p>0.05) in the presence of glucocorticoids, mimicking the steroid responsive phenotype of CLVS1 H510Y patients. Treatment with ROS inhibitors also rescued the reduced viability phenotype in CLVS1 KO podocytes.

Methods: To better understand the effects of the CLVS1 H510Y variant on podocyte homeostasis, we created human podocyte cell lines with CRISPR-Cas9 mediated heterozygous and homozygous CLVS1 H310Y knock-in (KI) mutations. We evaluated the KO and KI podocytes through automated live-cell imaging. Additionally, we further evaluated the effects of reduced CLVS1 function on podocyte function in vivo in zebrafish. Wild-type and mutant clavesin1 is expressed ubiquitously in zebrafish larval kidneys. CLVS1 knockout in cultured human podocytes. Additionally, transgenic H310Y KI KO displayed similar corticosteroid responsive phenotypes to CLVS1 KO lines, including increased apoptosis that could be rescued with ROS inhibition, while heterozygous KI lines were unaffected. Furthermore, we confirmed that the H310Y variant reduces binding to a critical antioxidant transporter, alpha tocopherol transfer protein (p=0.006), likely contributing to the ROS phenotypes. Electron microscopy analysis and quantification of excreted proteins revealed podocyte effacement and decreased glomerular filtration barrier integrity in zebrafish with knockdown of orthologous CLVS1 when compared to controls (p<0.0001).

Conclusions: Our data further demonstrates the importance of clavesin1 in the maintenance of podocyte viability and GFB integrity. It also suggests that oxidative stress regulation may be compromised in patients carrying pathogenic CLVS1 variants and highlights the potential for alternative therapies for NS patients that target ROS accumulation in podocytes.

Funding: Other NIH Support - NCICD, Commercial Support - Goldfinch Bio
PO1665
Spatial Transcriptomic Profiling of Collapsing Glomerulopathy
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Background: Collapsing glomerulopathy is a histologically distinct variant of focal and segmental glomerulosclerosis that presents with heavy proteinuria and portends a poor prognosis. Collapsing glomerulopathy can be triggered by viral infections such as HIV and SARS-CoV-2. However, it is not known if distinct molecular mechanisms drive histologically indistinguishable lesions of collapsing glomerulopathy in different clinical contexts.

Methods: Transcriptional profiling of collapsing glomerulopathy lesions is difficult since only a few glomeruli may exhibit this histology within a kidney biopsy. Therefore, we used recently developed spatial transcriptional profiling to quantify 1,852 transcripts in individual glomeruli from HIV and SARS-CoV-2 infected patients with biopsy confirmed collapsing glomerulopathy.

Results: We compared transcriptional signatures on the basis of disease or histology and identified distinct pathways of injury in HIV and SARS-CoV-2 associated collapsing glomerulopathy and thrombotic microangiopathy (Figure). Focused validation using RNA in situ hybridization showed good concordance with spatial transcriptional profiling results.

Conclusions: Spatial transcriptional profiling represents a powerful new method to dissect transcriptional programs of pathologically discernible kidney lesions.

PO1666
Protein Kinase R Inhibition Ameliorates Mitochondrial Dysfunction in the Tg26 HIV-Associated Nephropathy Mouse Model
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Background: Double-stranded RNA (dsRNA)-activated protein kinase (PKR) is a sensor for dsRNA in response to viral infections, including HIV-1. We previously reported that APOL1 risk alleles damage podocytes through double-stranded RNA-activated protein kinase (PKR) activation (Okamoto, Comm Biol, 2018). Here, we hypothesized that PKR activation could be a mechanistic pathway shared by HIV- and APOL1-mediated nephropathies. Hence, we investigated the effects of PKR inhibition on HIVAN in the well-characterized Tg26 mouse model, which expresses HIV regulatory and accessory genes.

Methods: We evaluated the kidney phenotype of Tg26 mice and wild-type mice treated with the PKR inhibitor (C16) from 6 to 12 weeks of age. We profiled kidney gene expression by RNA-seq and mitochondrial function by the extracellular flux assay using ex vivo glomerular tissues.

Results: Kidney disease manifestations, including albuminuria (mean [IQR]) (668 mg/g Cr [60, 1064] vs 2564 [1785, 5646], p=0.03) and global glomerulosclerosis (0.0% [0.0-0.0] vs 8.1 [2.3, 15.8], p<0.008), were reduced in the C16 treated group compared to the vehicle control group. C16 treatment increased mitochondrial gene expression and restored spare respiratory capacity as measured by extracellular flux assay (Fig. B).

Conclusions: PKR inhibition ameliorated mitochondrial dysfunction associated with the HIVAN phenotype observed in Tg26 mice, suggesting that PKR activation contributes to the development of mitochondrial dysfunction in HIVAN.

PO1667
Recurrent Nephrotic Plasma Activates Pro-Fibrotic Signalling Pathways Downstream of Protease-Activated Receptor 1
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Background: Post-transplant recurrence of steroid-resistant nephrotic syndrome (SRNS) is thought to be due to an unknown “circulating factor”, the identity of which has so far remained elusive. Our previous work suggests a signaling role for protease-activated receptor-1 (PAR-1), leading to impaired podocyte function. The signaling pathways downstream of PAR-1 in podocytes are unknown and could reveal novel mechanistic insights into the disease.

Methods: Conditionally immortalized human podocytes (ciPods), glomerular-like structure spheroids, and human kidney organoids were treated with PAR-1 agonist peptide or nephrotic plasma (NP), in the absence or presence of four different PAR-1 antagonists.

Results: PAR-1 agonist and patient relapse NP, but not paired remission plasma, induced the phosphorylation of VASP, JNK, and proteins involved in pro-fibrotic pathways. These changes were inhibited by PAR-1 inhibitors, but not by TGF-β1 inhibition. Four PAR-1 inhibitors demonstrated specific antagonistic properties. The phosphorylation of VASP and JNK in a 3D spheroid model and from stem-cell derived kidney organoids corroborated the finding from the 2D model. Functionally, relapse NP induced podocyte motility and podocyte loss from spheroids both of which were also selectively rescued by PAR-1 inhibitors. Treatment of kidney organoids with relapse NP induced the same VASP and pro-fibrotic phosphorylation in podocytes and the loss of podocyte-specific markers.

Conclusions: We propose that the circulating factor acts as a pro-fibrotic effector by activating PAR-1. A greater understanding of these signaling pathways will lead to the identification of novel therapeutic targets for this disease.

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PO1668

Molecular and Functional Characterization of Human Urinary APOL1 G2/G2 High-Risk Genotype Podocyte

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Background: Apolipoprotein L1 (APOL1) risk variants, G1 and G2, increase the risk of various non-diabetic kidney diseases in the African population. To date, the precise mechanisms by which APOL1 risk variants induce injury on podocytes and other kidney cells remain unclear. Trying to unravel these mechanisms, most studies used animal or cell models created by gene editing.

Methods: Conditionally immortalized human podocyte cell lines from urine of a donor carrying APOL1 high risk genotype, G2/G2 was developed. The APOL1 G2/G2 cell lines were characterized for podocyte markers at both the mRNA and the protein levels, using real-time quantitative PCR, Western blot and immunofluorescence staining. Following induction of APOL1 expression by 50 µg/mL polyinosinic-polycytidylic acid (poly(C)), we assessed the functional features of APOL1-induced podocyte dysfunction such as cell detachment, cell viability, cell death, autophagy, cytoskeleton organization and podocyte permeability. As control, APOL1 wild type (G0/G0) podocytes previously generated from a Caucasian donor were used.

Results: We successfully generated human APOL1 G2/G2 urinary podocyte cell lines. Upon exposure to poly(C), G2/G2 and G0/G0 podocytes upregulated APOL1 expression resulting in podocytes detachment, decreased cells viability and increased apoptosis rate in a genotype-independent manner. G2/G2 podocyte cell lines exhibited altered features, including upregulation of CD2AP, alteration of cytoskeleton, reduction of autophagic flux and increased permeability in an in vitro model under continuous perfusion.

Conclusions: The human APOL1 G2/G2 podocyte cell model is a useful tool for unraveling the mechanisms of APOL1-induced podocyte injury and the cellular functions of APOL1.

PO1669

Topology Mapping of Membrane-Inserted ApoL1

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Background: ApoL1 inserts into membranes at pH 6 where it has anion permease activity. Titration of the cis compartment to pH 7.5 suppresses the anion permease and activates a cation channel. How ApoL1 is arranged in the membrane-inserted form at various pH values is unclear.

Methods: Cys was substituted for Ser or Thr at positions throughout ApoL1 and resulting mutants expressed in E. coli. Purified mutants were allowed to insert into phospholipid vesicles at pH 6.0, held at pH 6.0 or titrated to pH 7.5, and reacted with extravesicular membrane-impermeant fluorescent Cys modifying reagent, Alexafluor-568-maleimide. Unreacted reagent was quenched. Non-membrane-inserted protein was removed by chaotropic extraction and Sepharose 4B chromatography. Membrane-associated protein was separated on SDS-PAGE along with ApoL1 standards for quantification. Ratio of fluorescence intensity to mass of ApoL1 protein was normalized to that of protein modified after detergent denaturation to determine relative accessibility of each Cys to the modifying reagent.

Results: Cys substitutions were generated at amino acid positions 40, 80, 149, 173, 186, 200, 204, 226, 247, and 365. We found three patterns of reactivity after membrane insertion. Cys at positions 40, 149, and 365 showed reactivity that was roughly comparable to that in detergent solution with little difference between pH 6.0 and 7.5, consistent with exposure to the aqueous solution on the cis face of the membrane under all conditions. In contrast, Cys at positions 186, 226 and 247 showed decreased reactivity after membrane insertion that was similar at both pH 6.0 and pH 7.5; these positions are not fully accessible from the external solution. Finally, Cys at positions 80, 173, 200, and 204 had decreased reactivity at pH 6.0 with increase in reactivity at pH 7.5, suggesting these positions may be initially buried in the membrane upon insertion at low pH, but titration to neutral pH induces a structural transition that exposes them to the external solution.

Conclusions: Mapping accessibility of individual amino acid positions in ApoL1 support a model in which a substantial structural transition accompanies the pH shift-induced activation of the cation channel.

Funding: NIDDK Support

Relative reactivity of membrane-inserted cysteine substitution mutants at pH 6.0 or 7.5
PO1671

Podometrics in Different Cortical Zones and Associations with the Number of Non-Sclerotic Glomeruli

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Background: Reduced nephron and podocyte number are common features in CKD. While it is well known that glomerular volume and glomerular density (glomerular number per cortical area) differ between cortical zones, zonal differences in podometrics and correlations with nephron number have not previously been explored.

Methods: Non-sclerotic glomerular number per kidney was estimated using the physical disector/fractionator combination. Podocyte density, podocyte number, podocyte volume and volumetric density of podocyte to glomerulus in each cortical zone were estimated using model-based stereology on a single histological section immunostained with two podocyte markers and imaged by confocal microscopy.

Results: Fifty autopsy kidneys were studied. The median age was 68 years ranging from 28 to 85 years. Median eGFR was 74 mL/min/1.73m². The median number of non-sclerotic glomeruli per kidney was 421,547 (IQR, 289,095−638,233). Non-sclerotic glomerular number was directly correlated with podocyte number per tuft, podocyte density and volumetric density of podocytes in each cortical zone (Fig). Glomeruli in the superficial cortex were smaller than glomeruli in other zones and had the highest podocyte density and volumetric density of podocytes (Fig). Glomerulosclerotic index (GSI).

Conclusions: These results demonstrate for the first time that a higher number of non-sclerotic glomeruli is directly associated with three beneficial indices of podocyte and glomerular health. Podocyte number and volumetric density of podocytes were more reliable indicators of non-sclerotic nephron number, independent of cortical zones.

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PO1672

Can Podocyte Number and Density Predict the Response to Therapy in Patients with Primary FSGS?

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Background: Podocyte loss is a key event in primary focal segmental glomerulosclerosis (FSGS). Common first-line therapy for patients with primary FSGS involves steroid therapy with or without blood pressure control; however 40-70% of patients achieve no remission. Animal studies have shown that treatment efficacy is achieved partly through preservation of podocyte number, as well as podocyte protective effects. Animal studies have also determined that podocyte number and density are predictive of FSGS severity. Therefore, this study aimed to determine if podocyte number and density can predict the response to therapy in patients with primary FSGS.

Methods: A retrospective cohort study of renal biopsies was conducted from 2009-2020 in Melbourne, Australia at a tertiary hospital (Monash Medical Centre). Patients diagnosed with primary FSGS were screened (n=84). Patients were excluded for lack of consent for samples to be used for research purposes (n=38), risks of other forms of FSGS (n=13), insufficient clinical data available (n=2), no biopsy tissue available (n=7) or <6 glomerular profiles available in the biopsy (n=5). Included patients were allocated into groups of treatment responders (n=11) or non-responders (n=8) based on urinary/serum data 6 months following initial diagnosis and commencement of treatment. Biopsies were immunofluorescently stained for podocyte-specific markers. Model-based stereology was used to estimate podometrics. Sections were re-stained with PAS to measure the glomerulosclerotic index (GSI).

Results: Podocyte number per glomerulus in responders (347 (215-606); median (IQR)) was 45% higher than in non-responders (190; 143-263) (P=0.03). Podocyte density in responders (76; 58-142 per 10⁶ of glomerular volume) was similar to non-responders (66; 44-88 per 10⁶ of glomerular volume) (P=0.38). GSI was significantly higher in non-responder patients (1.1; 0.6-2.3) than responders (0.6; 0.2-0.9) (P=0.04), and was significantly and negatively correlated with podocyte number (r = -0.64; P=0.003) and podocyte density (r = -0.48; P=0.04).

Conclusions: Podocyte number per glomerulus in diagnostic renal biopsies could be used as a predictor of treatment response for patients with primary FSGS.

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PO1673

Nephrotic Syndrome in a Patient with Systemic Lupus Erythematosus: Is it Lupus Podocytopathy?

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Introduction: Lupus podocytopathy (LP) is a rare form of lupus nephritis (LN) that clinically mimics minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). We present a case of LP in a patient with systemic lupus erythematosus (SLE). Case Description: A 73-year-old female with a history of SLE (on Hydroxychloroquine), and nephrolithiasis presented with left flank pain for 2 weeks. Physical exam was notable for peripheral edema and left costovertebral angle tenderness. Labs showed a creatinine 1.02 mg/dL (baseline 0.7), serum albumin 2.6 mg/dL, and urine microalbumin/creatinine (MA/Cr) ratio of 7.5 g/g. Further workup revealed a positive ANA, negative anti-dsDNA antibodies, and normal complements. Kidney biopsy showed FSGS, tip variant, and 100% podocyte foot process effacement (FPE). She was started on high-dose prednisone, simvastatin, ACE inhibitor, and furosemide with potassium supplementation for significant pedal edema. Two months later, her MA/Cr ratio improved to 3 g/g. Prednisone was slowly tapered off over a 7-month period during which symptoms were well-controlled and MA/Cr ratio continued to improve.

Discussion: Nephrotic syndrome in patients with SLE raises suspicion for LP, which represents 1% of LN biopsies. Biopsy findings include diffuse FPE (>70%) on electron microscopy, and absence of immune deposits on light, immunofluorescence, and electron microscopy. LP is divided into MCD or FSGS, with the latter having higher rates of hypertension, acute kidney injury on presentation, and overall worse outcomes. Treatment consists of a short course of high-dose glucocorticoids; however high rates of relapse are observed and tend to coincide with SLE activity.
PO1674

Minimal Change Disease as a Sequela of Psoriasis in an Adult
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Introduction: Minimal change disease (MCD) is usually found in children but can be an uncommon presentation in adults. Relation to psoriasis has not been significantly established even though the latter has been associated with kidney disease such as IgA nephropathy, focal segmental glomerulosclerosis leading to kidney failure. This is an interesting case given that this is a young patient with psoriasis presenting with a flare in the setting of newly diagnosed MCD.

Case Description: A 34-year-old male with history of psoriasis presented with severe body edema after psoriatic flare two weeks prior admission. He was found to have exceptionally low serum albumin of 1.4g/dL, massive proteinuria with spot urine protein creatinine ratio of 7.6 and significant hyperlipidemia. Protein electrophoresis did not show glomerular pathology or spikes in proteins and extensive serological workup was normal. Kidney biopsy reported MCD. Patient improved quickly with steroids of 1mg/kg/day, IV furosemide and albumin infusion. Six months later, the patient was readmitted with new psoriasis flare and again nephrotic syndrome with 7.2g of proteinuria. His symptoms resolved quickly with same treatment used on the first admission. Follow up in clinic one-month post discharge showed normal renal function with proteinuria now at 100mg/day.

Discussion: While there has been evidence of link between psoriasis and kidney disease, finding of MCD is a unique development. The idea can be postulated that since psoriasis is a disease due to dysfunction of T-cells among other causes, a flare can be the initiating event leading to dysregulation of an otherwise stable immune system. This T-cell dysregulation has also been noted in MCD. The underlying cause of MCD is not clear. However, a lot of studies suggest that T-cell dysfunction is one of the implicated agents, known for cell destruction, causing damage to the glomerular membrane leading to the loss of proteins. The rarity of this case belies the complexity of the immunological process leading to the presentation and further research needs to be done to document and establish this as the pathologic process linking the two diseases.

PO1675

Collapsing FSGS from Acquired Nephrin Antibody
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Introduction: Deficits in nephrin and other podocyte components are known to result in congenital nephrotic and familial FSGS syndromes. Weins et al. recently described acquired anti-nephrin antibody localizing in glomerular podocytes of patients with minimal change disease.

Case Description: A 16 year old male referred for new onset nephrotic syndrome progressive over 2 weeks was found to have serum albumin 1.2 gm/dL, UPCR 3.1, and elevated lipids with BP 160/100 mm Hg. Hepatitis B/C, HIV, SLE screens were negative. Renal biopsy demonstrated focal collapsing lesions with diffuse podocyte effacement. Immunofluorescence showed punctate IgG, kappa and lambda light chain staining in podocytes, but no albumin. Anti-human IgG colocalized with nephrin in the granular staining. ParvoB19 and COVID-19 titers were negative. Creatinine rose from 0.65 to 1.65 and UPCR to 10.3 but improved rapidly with high dose prednisone and ACEI. Serology for circulating anti-nephrin 2 weeks into treatment was negative, consistent with previous finding that circulating antibody levels quickly drop to low or undetectable with partial clinical remission.

Discussion: This case strengthens evidence that anti-nephrin antibodies cause disruption of the slit pore diaphragm which appears to be readily responsive to immune therapy. Anti-nephrin mediated podocytopathy may present with a spectrum of glomerular histopathology, which on the background of other susceptibility factors, can lead to more severe presentations such as collapsing FSGS.

PO1676

Anti-Nephrin Autoimmunity in Early Primary FSGS
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Introduction: Minimal change disease (MCD) and primary FSGS are important diagnoses in adults and children with acute nephrotic syndrome (NS). We have reported anti-nephrin-mediated autoimmunity in NS with MCD on kidney biopsy (KBx). Here, we describe a patient with KBx-proven diagnosis of early primary FSGS and persistent anti-nephrin IgG in glomeruli and serum.

Case Description: A 69yo Caucasian man with history of type 2 DM presents with acute kidney injury (6Cr 3.49g/dl), anasarca, hyperlipidemia, s Alb 3.8g/dL, UPCR 18g/gCr. Serologies including ANA, HIV, anti-PLA2r are negative; FLC ratio is 2.91. A kidney biopsy is ordered; the differential diagnosis includes MCD, membranous nephropathy, FSGS and paraprotein-related diseases. The biopsy contains 52 glomeruli with 12% global sclerosis, and 2 glomeruli with early segmental sclerosis with capillary collapse, epithelial hyperplasia and protein reabsorption granules (PRGs). Diabetic glomerular changes are not seen. Tubular atrophy and interstitial fibrosis are mild, and vascular sclerosis is moderate to severe. Immunofluorescence microscopy (IF) shows trace mesangial IgM and fine granular podocyte IgG with equal kappa/lambda. Electron microscopy reveals diffuse podocyte foot process effacement without deposits and loss of

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522
Nephrotic Syndrome Secondary to Minimal Change Disease Following Moderna COVID-19 Vaccine

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Introduction: Minimal Change Disease (MCD) has been reported following vaccines against hepatitis, pneumococcus, influenza and measles. In the COVID-19 era, 3 cases of new-onset MCD and one case of MCD relapse have been reported following the Pfizer-BioNTech COVID-19 vaccine. We herein report a case of MCD after receiving the first dose of Moderna COVID-19 vaccine.

Case Description: A 43-year-old Ethiopian man with no significant past medical history presented with progressive bilateral lower limb edema for two weeks. His symptoms started 7 days after receiving the first dose of COVID-19 vaccine. He then developed dyspnea and scrotal swelling over the following 10-14 days. On physical examination, his blood pressure was 150/92 mm Hg. There was decreased air entry at lung bases, significant bilateral lower limb pitting edema extending to above the knees and scrotal swelling. Lab investigations revealed hypoalbuminemia, hyperlipidemia and proteinuria of 15 grams. There was no hematuria and his immunologic and serologic work up was negative. Renal biopsy showed minimal change disease with underlying IgA nephropathy. There was no global or segmental glomerulosclerosis, mesangial or endocapillary proliferation. Patient was started on oral prednisolone and furosemide. His edema resolved, serum albumin doubled and proteinuria decreased within the first week of treatment.

Discussion: Symptoms of MCD have been reported 4 days to 16 weeks after vaccination. Although the pathogenesis of MCD is not fully understood, studies suggest that T-cell dysfunction might play a role. More studies are needed to determine the incidence and pathophysiology of this adverse event post COVID-19 vaccine. It is not clear in this case if or when the second dose of the COVID-19 vaccine should be administered.

PO1678

Antiproteinuric and Podocytoprotective Effects of Direct Oral Anticoagulant Therapy in Glomerular Disease

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Background: Podocyte injury is a key determinant of chronic kidney disease (CKD) progression toward end stage kidney disease. We and others have recently uncovered a putative podocytopathic role for intraglomerular thrombin during proteinuric glomerular disease. Direct oral anticoagulant (DOAC) therapies limit thrombin activity but their ability to improve podocyte health and potentially slow CKD progression remains unknown. Thus, the aim of this study is to determine if DOACs reduce thrombin-mediated podocytopathy during glomerular proteinuria. We hypothesized that DOACs would preserve podocyte health and function in a podocyte-specific model of proteinuric glomerular disease.

Methods: Diphtheria Toxin was used to induce proteinuria in transgenic rats expressing human diphtheria toxin receptor (DTR) in a podocyte-specific manner and was subsequently treated with 1) Dabigatran (20 mg/kg; Dabi), 2) Rivaroxaban (3 mg/kg; Riva), or 3) Sham (saline) and compared to healthy controls (n=7-9/group). Morning spot urine was collected on day 0 and 10 post-DT. Glomeruli were isolated from the kidney, dissociated into single-cell suspensions, and analyzed by flow cytometry after immunofluorescent synaptopodin antibody and TUNEL staining.

Results: Both Dabi and Riva significantly reduced proteinuria (Fig A) and terminal podocyte injury (TUNEL positive podocyte fraction; Fig B). In addition, there was a trend toward in situ podocyte preservation with both DOACs with a significant overall effect of DOAC therapy on podocyte survival (Fig C).

Conclusions: Both Dabi (a direct thrombin inhibitor) and Riva (a direct factor Xa inhibitor) reduce proteinuria and enhance podocyte health in a podocyte-specific model of proteinuric glomerular disease. These data suggest that DOACs may be repurposed as a novel approach to slow or halt proteinuric glomerular disease progression. Because thrombotic disease is a life-threatening co-morbidity of both glomerular disease and CKD, this approach may enable simultaneous thromboprophylaxis and glomerular disease therapy.

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PO1679

A Highly Efficient and Reproducible Differentiation Protocol for Induced Pluripotent Stem Cell-Derived Podocytes

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Background: Podocyte processes intertwine to create a slit diaphragm, which, when imbalanced, leads to proteinuria, dysfiltration, and, eventually, to renal failure. It is critical to be able to study the disease and test therapeutic interventions in patient-derived cells, and assess genetic and environmental aspects. Current protocols for differentiation of iPSCs into podocytes (iPods) suffer from a lack of podocyte maturity or low reproducibility. Our goal was to test and optimize multiple protocols to establish a more translatable, physiologically relevant, and reproducible method.

Methods: We compared two distinct published protocols [Ciampi 2016; Mulsat 2018]. Additional conditions were tested, including varying the extracellular matrices, media, and length of differentiation. Podocyte signature was evaluated by IF, flow cytometry, and Nanostring analysis. For models of injury, we utilized proline transamine (PS) or purinergic annomusinoicid (PAN) treatment. A mouse podocyte cell line was used as a control.

Results: Both protocols generated iPods with similar efficiency, as measured by synaptopodin, nephrin and podocin staining. iPods generated from protocol-1 could be maintained in culture up to 14 days but remained relatively immature, based on the expression of collagen α1(IV) and lack of collagen α3(IV). Response to PS and PAN treatment was variable compared to mouse podocytes. Altering the matrix from collagen to laminin did not improve reproducibility. iPods from protocol-2 developed more filopodia and complex cell-cell junctions and appeared more homogenous, with extended survival up to 4 weeks post-differentiation. PS treatment induced a significant and reproducible dose- and time-dependent decrease in synaptopodin expression, and a more robust accumulation of phalloidin aggregation. Both effects were effectively prevented by cyclosporin A, a calcineurin inhibitor, in a similar manner as in mouse podocytes. iPods from protocol-2 also showed a more consistent dose-dependent response to PAN injury.

Conclusions: We achieved a more robust and translatable iPod platform utilizing human iPSCs. Patient-derived iPodos will be an invaluable tool for both research and clinical applications.

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PO1680

Novel Ex Vivo Culture System Reveals Mechanosensitive “Sarcocere-Mike Structures” During Early Podocyte Spreading

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Background: Chronic kidney disease and ESKD are widespread health problems with no cure, in part because the biophysics underlying them are still not clear. A recently discovered feature of injured podocytes includes the de novo assembly of sarcocere-like stress fibers, identified by their alternating myosin and synaptopodin-a-actin-4. It is not known whether these indicate a transient healing phenotype or are a feature of the cascade leading to foot process effacement.

Methods: To model the early events of podocyte injury, we developed a novel in vitro system that enables the study of podocytes outside of their native microenvironment, but with in vivo-like mechanobiological and extracellular matrix (ECM) features. This system includes controllable stiffness, micro-patterned substrates for spreading, and the use of primary podocytes as they migrate from freshly isolated glomeruli.

Results: When cultured on micropatterns of physiologically relevant extracellular matrix proteins and appropriate stiffness, myosin- and synaptopodin-positive stress fibers develop. Two days of culture, then disappeared after six days, and the appearance of these stress fibers was sensitive to substrate stiffness and could be disrupted by inhibiting actomyosin contraction (blebbistatin), culturing cells with stiffness outside of the physiologic range, or presenting cells with substrates associated with pathology.

Conclusions: These results reveal the role of mechanobiological factors in podocytes represented by the mechanoresponsive sarcocere-like structure and establish a novel system for characterizing this mechanobiology in vitro.

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PO1681

Primary Cilia in Podocyte Health and Disease

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Background: Primary cilia are highly specialized elaborations of the plasma membrane that direct many of the signaling cascades critical for pre- and post-natal development and disease. While renal primary cilia are recognized as key genetic and cellular targets in polycystic kidney disease, the presence and function of primary cilia within the renal corpuscle and glomerulus have yet to be fully characterized. The purpose of our study was to perform a focused and quantifiable characterization of primary cilium of glomerular cell populations in health and disease.

Methods: Renal biopsy samples were obtained from patients with Minimal Change Disease (MCD; N=6), Focal Segmental Glomerular Sclerosis (FSGS; N=5), and control renal tissue (CON; N=4). Immunofluorescence analyses (IF) were used to quantify primary cilia number and length, as well as the expression of Sonic Hedgehog (SHH) protein, the ligand component of the Hedgehog signaling pathway and one measure of primary cilia function.

Results: Mean percent ciliation was significantly increased in MCD and FSGS when compared to CON. Analysis of individual glomerular primary cilia revealed increased ciliary length (µm) in both MCD and FSGS when compared to CON. Further analysis comparing primary cilia length in WT-1-positive nuclei (WT-1+; podocytes) also revealed a pronounced increase in cilia length in MCD and FSGS podocyte primary cilia versus CON. Despite increased length of primary cilia, glomerular SHH expression was significantly decreased in both MCD and FSGS when compared to CON. Glomerular diseases MCD and FSGS are therefore associated with an overall increase in podocyte primary cilia length and ciliation, an effect which corresponded to a decrease in SHH expression.

Conclusions: These data provide evidence in support of a role for primary cilia in glomerular disease pathogenesis. Ongoing and future research is needed to establish a mechanistic explanation for these changes observed in glomerular and podocyte cilia number and length. A more thorough understanding of the role(s) of primary cilia in glomerular cells, and specifically in podocytes, remains critical for both our understanding of disease pathogenesis as well as for the pharmacologic treatment of glomerular chronic kidney disease.

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524
of cytotoxic sheep anti-glomerular antibodies (or media alone as control) for 2 hours. The two groups were kept at room temperature to allow immunoprecipitation for 1 to 4 days. Diffusion calculations suggested moderate sized (10 kDa) signaling molecules take approximately 2 days to reach the other chamber. Immunocytochemistry characterized podocyte injury and PEC activation and epithelial-mesenchymal transition (EMT).

Results: Podocyte foot processes, accompanied by a dose-dependent increase in the de novo expression of the injury marker desmin. In contrast to F-actin staining of the control group exhibiting thick bundles of actin, podocytes with Fc-CLEC-2 showed a round morphology and GTPase activation was not altered. In addition, we also studied the impact of elevated Piezo levels and could show, that in line with the YODA effect, Piezo overexpression revealed severely increased Rho1-GTP levels and FITC uptake, while morphology was not changed. Because of this severe pathological phenotype, we tried to rescue the effects of Piezo overexpression with pharmacological inhibition by using tarantula toxin. Intriguingly, treatment with tarantula toxin reversed the elevated Rho1-GTP levels observed upon Piezo overexpression.

Conclusions: Taken together, our data confirms the functional expression of Piezo in nephropathy, its role in regulating GTPases and the beneficial effect of tarantula toxin to reverse the pathological effects caused by increased Piezo levels.

PO1685

The Mechanosensitive Ion Channel Piezo Activates Rh1 in Drosophila Nephrocytes

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Background: Podocytes constantly face biomechanical forces such as shear stress and hydrostatic pressure. Increasing forces result in morphological changes, detachment from the glomerular basement membrane and loss into the primary urine. This highlights a requirement for podocytes to sense changes in their physical environment and induce a response to react to increased biomechanical force.

Methods: Here, we investigated the functional role of the mechanosensitive ion channel Piezo in Drosophila nephrocytes.

Results: First, we confirmed Piezo expression and localisation at the nephrocyte diaphragm. Additionally, we investigated the role of Piezo in nephrocytes and delineating the putative Piezo mechanosensitive pathway. For further analysis, we used knockout flies and observed a filtration phenotype, while morphology and GTPase activation was not altered. In addition, we also studied the impact of elevated Piezo levels and could show, that in line with the YODA effect, Piezo overexpression revealed severely increased Rho1-GTP levels and FITC uptake, while morphology was not changed. Because of this severe pathological phenotype, we tried to rescue the effects of Piezo overexpression with pharmacological inhibition by using tarantula toxin. Intriguingly, treatment with tarantula toxin reversed the elevated Rho1-GTP levels observed upon Piezo overexpression.

Conclusions: Taken together, our data confirms the functional expression of Piezo in nephropathy, its role in regulating GTPases and the beneficial effect of tarantula toxin to reverse the pathological effects caused by increased Piezo levels.

PO1686

Drosophila Filamin Exhibits a Mechanoprotective Role During Nephrocyte Injury via Hypertrophy

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Background: Podocytes are constantly exposed to biomechanical forces such as shear stress and hydrostatic pressure. These forces increase during disease like diabetes and hypertension, resulting in adaptive mechanisms such as podocyte hypertrophy. But how do podocytes sense changes in biomechanical forces and how does the molecular response look like?

Methods: To investigate this, we utilized Drosophila nephrocytes and studied the functional role of the mechanosensor Cheerio (dFilamin). FilaminB is upregulated in podocyte injury models and upon increased biomechanical stress, therefore serving as an ideal candidate for mediating mechanoprotection in response to injury.

Results: Expression of an over-active mechanosensor region variant of Cheerio resulted in a significant hypertrophy phenotype, while morphology and filtration function were only mildly affected. Interestingly, the expression of over-active Cheerio caused a rescue of filtration function after depletion of the nephrocyte diaphragm proteins Duf (dNEPH) and Sns (dNeph). Additional analysis with human FilaminB confirmed this mechano-protective role and the involvement of the mechanosensor region in the hypertrophy phenotype. To delineate the mechanoprotective pathway acting downstream of FilaminB, we studied the candidates: TOR, WNT and YAP. Activation of these pathways result in nephrocyte hypertrophy. Interestingly, TOR repression reversed the hypertrophy in over-active Cheerio expressing cells, suggesting TOR to be a novel downstream target of Cheerio and to be responsible for the hypertrophy phenotype.

Conclusions: Although Cheerio and FilaminB mediate a mechanoprotective role in the face of injury, their excessive expression resulted in a severe morphological and functional phenotype, emphasizing the need of a tight control of expression levels.

PO1683

Membrane Localization and CLIC5A-Stimulated Rac1 Activation in Podocytes

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PO1684

A Direct CLIC5A/Ezrin Interaction Accounts for CLIC5A Plasma Membrane Localization and CLIC5A-Stimulated Rac1 Activation in Renal Glomeruli


Background: CLIC5A is a part of the Podocalyxin/Ezrin complex at the apical domain of podocyte foot processes. Ezrin binds membrane phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) inducing its activation and C-terminal (T567) phosphorylation. Activated Ezrin bridges membrane-spanning proteins to cortical actin, shaping the cellular architecture. We reported that CLIC5A stimulates Rac1-GTP-dependent PI(4,5)P2 generation and Ezrin activation and that CLIC5A deleteriously affects the pERM and podocalyxin confirming dephosphorylation of ERM in podocytes. CLEC-2, the endogenous ligand of podoplanin, is highly expressed in platelets and also exists in the plasma as a soluble form. Normally, podocytes are sequestered from CLEC-2, but when the glomerular barrier is injured, podocytes can have access to CLEC-2. We studied potential actions of CLEC-2 on podocytes.

Methods: First, we confirmed Piezo expression and localisation at the nephrocyte diaphragm. Additionally, we investigated the role of Piezo in nephrocytes and delineating the putative Piezo mechanosensitive pathway. For further analysis, we used knockout flies and observed a filtration phenotype, while morphology and GTPase activation was not altered. In addition, we also studied the impact of elevated Piezo levels and could show, that in line with the YODA effect, Piezo overexpression revealed severely increased Rho1-GTP levels and FITC uptake, while morphology was not changed. Because of this severe pathological phenotype, we tried to rescue the effects of Piezo overexpression with pharmacological inhibition by using tarantula toxin. Intriguingly, treatment with tarantula toxin reversed the elevated Rho1-GTP levels observed upon Piezo overexpression.

Conclusions: Taken together, our data confirms the functional expression of Piezo in nephropathy, its role in regulating GTPases and the beneficial effect of tarantula toxin to reverse the pathological effects caused by increased Piezo levels.
PO1687

Characterization of a Novel FSGS-Associated ACTN4 Mutation in Drosophila melanogaster


Background: Decisive for podocyte morphology and homeostasis during health and disease is a specialized and highly regulated organization of the actin cytoskeleton. In this context, the actin cross-linking protein Alpha-actinin4 (ACTN4) has been shown to play a crucial role in podocyte architecture and function. Mutations in the ACTN4 gene are associated with focal segmental glomerulosclerosis (FSGS). Here, performing gene panel sequencing in a pediatric patient presenting with steroid resistant nephrotic syndrome and FSGS, a de novo, potentially disease causing variant of ACTN4 was identified, which was previously undescribed and not found in available genome or exome databases. Our aim is to elucidate the pathogenic potential of this variant for podocytes and FSGS progression.

Methods: To elucidate pathogenic effects of the newly identified ACTN4 variant, we employed the genetic toolbox of Drosophila. The fly holds podocyte-equivalent cells called nephrocytes, which are responsible for filtration and detoxification of the hemolymph. Cell-specific genetic manipulation enabled us to analyze RNAI-mediated knockdown of Actinin, the single fly homolog, in nephrocytes and its impact on cell morphology and function. Rescue experiments with the novel human ACTN4 variant will now reveal whether or not possible pathogenic consequences of the mutation when compared to wildtype as well as previously described disease-associated variants of ACTN4.

Results: Knockdown of Drosophila Actinin in nephrocytes leads to severe functional impairment, reduced cell-cell contact and up to 50% mislocalization of the ZO-1 homolog Polychoactid as observed well as overall reduction of nephrocyte diaphragms. First rescue experiments with wildtype human ACTN4 led to partial rescue of functional and morphological phenotypes observed upon Actinin knockdowns.

Conclusions: Our results underline the importance of Actinin for nephrocyte biology. Capacity of wildtype human ACTN4 in rescuing the knockdown associated phenotypes indicates the model’s suitability. Further experiments will be performed to elucidate the pathogenic potential of the novel ACTN4 variant also in comparison to previously described pathogenic mutations.

PO1689

Selective PPARγ Modulator with Reduced Adipogenic Potential Ameliorates Experimental Nephrotic Syndrome

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Background: Glomerular disease, often manifesting as nephrotic syndrome (NS) with high proteinuria, can be refractory to standard treatment and is typically associated with hypoalbuminemia, hyperchloremia, and hypercoagulopathy. We hypothesized that the nuclear receptor PPARγ can be selectively modulated using a novel partial agonist, PQ-16, to gain therapeutic advantage over traditional PPARγ agonists for NS treatment.

Methods: Pio and PQ-16 were administered daily to male Wistar rats with puromycin amine-nucleoside (PAN)-induced nephropathy. Serum and urine chemistries were performed and kidneys, glomeruli, liver, and white adipose tissue (WAT) were harvested for RNA and protein extraction. Blood was collected for determination of thrombin generation parameters.

Results: PAN induced robust proteinuria, which was significantly reduced with Pio to 64% of PAN-value, and robustly with PQ-16 to 81% of PAN, which was comparable to controls. Podocyte hypertrophy also returned to normal with Pio and PQ-16. While both Pio and PQ-16 lowered 38.1 vs 85.9 ± 7.8 CaSR positive

PO1690

Simultaneous Loss of Podocyte Insulin Receptor (IR) and Insulin-Like Growth Factor 1 Receptor (IGF1R) Is Detrimental and Associated with Spliceosome Dysfunction

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Background: Insulin signalling to the podocyte via the insulin receptor (IR) is crucial to podocyte function. Insulin-like growth factor 1 (IGF1) signalling through the structurally related insulin-like growth factor 1 receptor (IGF1R) is also known to directly affect the podocyte. Since the IR and IGF1R may act redundantly in some contexts, this study sought to elucidate the compound role of the insulin/IGF1 axis in podocyte function using mouse and cell culture models deficient in both receptors.

Methods: To examine the effects of combined receptor loss in vivo, a transgenic mouse model with conditional inactivation of podocyte IR and IGF1R was generated. In vitro, conditionally immortalised genetic IR knockout, IGF1R knockout and IR/IGF1R dual knockout podocytes were characterised using global proteomic and transcriptomic analysis.

Results: Podocyte specific IR/IGF1R knockout mice developed significant albuminuria and a severe renal phenotype with global sclerosis, renal failure and death occurring between 4 and 24 weeks. -90% loss of IR/IGF1R in cultured mouse podocytes was also detrimental resulting in >50% cell death 7 days after gene knockdown. Enrichment analysis of total proteomic data revealed a striking downregulation of gene ontology terms associated with splicing and RNA processing activity in IR/IGF1R knockout cells. Western blot analysis was used to validate the reduced expression of proteins responsible for spliceosome synthesis and regulation in dual knockout podocytes, including polyypyrimidine tract-binding protein 2 (PTBP2), eukaryotic initiation factor 4A (EIF4A) and splicing factor 3B subunit 4 (SF3B4).

Conclusions: This work underlines the critical importance of podocyte insulin/IGF signalling and reveals a novel role for this signalling axis in RNA processing by regulating spliceosome activity.

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PO1691
Regression of Severe Preexisting Glomerular Pathology in a Mouse FSGS Model in Response to Treatment with Macula Densa-Derived Biologicals
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Background: Macula densa (MD) cells localized at the glomerular vascular pole synthesize and release numerous vasoactive autacoids and newly identified angiogenic (e.g. CCN1) and glomulotrophic factors that act in a paracrine fashion to maintain high renal/glomerular blood flow and endogenous tissue remodeling. The present study aimed to test the tissue regenerative therapeutic potential of MD-derived biologicals in vivo in a mouse model of focal segmental glomerulosclerosis (FSGS).

Methods: BalbC mice with Adriamycin-induced stable, severe FSGS and albuminuria (albumin/creatinine ratio ACR>10,000/gm) were randomized into 3 groups and started daily ip injections (150µl each) of either saline (S), human recombinant (hr) CCN1 in low-dose (0.3 ng/mouse), L, hrCCN1 high-dose (2µg/mouse), H, and dextrane(F12 control, D), and conditioned culture media of the new MD cell line mMDR+ (MD) for 4 weeks. Transcutaneous GFR (MediBeacon) and ACR were measured weekly. Terminal histological analysis was performed using PAS and Trichrome staining.

Results: Kidney injury was severe at the onset (GFR 1160±51 mL/min/100 g BW, ACR 1322±159, and was sustained throughout the 4 weeks of treatment in control S and D groups (GFR 1080±143, 992±164, ACR: 1022±75, 369, 358±163, respectively).

In contrast, a progressive and significant improvement in kidney function was observed against doxorubicin-induced cell death whilst wild-type podocytes treated with PPP proteins involved in cell death and those that directly interact with CaMK4 in FSGS.

Selecting target molecules that improve outcomes in the presence of adriamycin and glomerulosclerosis (FSGS), but the involved mechanisms remain poorly understood. Calcium/calmodulin kinase 4 (CaMK4), a serine threonine kinase, is increased in podocytes of people with FSGS and in mice models of FSGS. Result: we found that lack of CaMK4 in podocytes suppressed the development of kidney pathology including the presence of hyaline deposits in glomeruli, podocytopenia and tubulointerstitial damage with intratubular casts in mice injected with adriamycin. Proteinuria in mice lacking CaMK4 in podocytes exposed to adriamycin, was reduced at 7 days and remained low through the 14th day when compared to control mice. Mechanistically we found that CaMK4 phosphorylates 14-3-3, releasing pro-apoptotic protein BAD which in turn binds to the antiapoptotic protein BCL-2, thereby allowing BAX, to aggregate on mitochondria and induce release of cytochrome c through mitochondrial pore formation, followed by caspase activation and apoptosis. In parallel, CaMK4 inhibits autophagy, a process needed for the renewal of damaged organelles, through the mTOR pathway, by directly phosphorylating AKT and S6 kinase.

Conclusions: We demonstrate that mice lacking CaMK4 specifically in podocytes are protected from FSGS-like disease after exposure to adriamycin. These mice also demonstrate markedly reduced proteinuria and podocytopenia. We found that apoptosis leads to cell death while autophagy is protective in FSGS. The characterization of the specific molecular events which lead to podocyte loss and glomerulosclerosis point to putative therapeutic targets and biomarkers for FSGS.

Funding: NIDDK Support.

PO1692
Insulin-Like Growth Factor 1 Receptor (IGF1R) Suppression in the Glomerular Podocyte Has Beneficial and Detrimental Consequences Dependent on the Level of Inhibition
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Background: Insulin signaling to the glomerular podocyte via the insulin receptor (IR) is known to be critical for normal kidney function. This study aimed to define the physiological importance of the closely related insulin-like growth factor 1 receptor (IGFIR) in podocytes.

Methods: Transgenic mice with conditional inactivation of podocyte IGFIR were generated to determine the effects of IGFIR suppression in vivo. In vitro, conditionally immortalised genetic IGFIR knockout and wild-type podocytes treated with the IGFIR inhibitor pircopodophilppin (PPP) were characterised using global proteomic analysis.

Results: Transgenic mice with partial podocyte-specific IGFIR knockout, generated using conventional Cre recombinase, had no apparent basal renal phenotype but unexpectedly, were protected from doxorubicin-induced nephropathy. An additional mouse model using an epigenetically resistant podocyte Cre driver designed to increase CaMK4 inhibits autophagy, a process needed for the renewal of damaged organelles, through the mTOR pathway, by directly phosphorylating AKT and S6 kinase.

Conclusions: We demonstrate that mice lacking CaMK4 specifically in podocytes are protected from FSGS-like disease after exposure to adriamycin. These mice also demonstrate markedly reduced proteinuria and podocytopenia. We found that apoptosis leads to cell death while autophagy is protective in FSGS. The characterization of the specific molecular events which lead to podocyte loss and glomerulosclerosis point to putative therapeutic targets and biomarkers for FSGS.

Funding: NIDDK Support.

PO1693
Calcium/Calmodulin Kinase 4 Induces FSGS by Promoting Apoptosis While Inhibiting Autophagy in Podocytes
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Background: Podocyte injury and death precede the development of focal segmental glomerulosclerosis(FSGS), but the involved mechanisms remain poorly understood. Calcium/calmodulin kinase 4 (CaMK4), a serine threonine kinase, is increased in podocytes of people with FSGS and in mice models of FSGS.

Methods: B6, B6 CDMK4fl/fl.podocite-ir or CDMK4fl/fl.podocite-ir mice were created and injected with i.v. adriamycin. Urine was collected on days 0, 3, 7, or 14, and kidney samples were collected on day 7 or 14 after adriamycin injection. Cultured human podocytes in the presence and absence of CAMK4 inhibitor (KN93) were exposed to adriamycin after which immunofluorescence and western blot was performed. Pull down mass-spectrometry and co-immunoprecipitation analysis was performed to identify proteins involved in cell death and those that directly interact with CaMK4 in FSGS.

Results: We found that lack of CaMK4 in podocytes suppressed the development of kidney pathology including the presence of hyaline deposits in glomeruli, podocytopenia and tubulointerstitial damage with intratubular casts in mice injected with adriamycin. Proteinuria in mice lacking CaMK4 in podocytes exposed to adriamycin, was reduced at 7 days and remained low through the 14th day when compared to control mice. Mechanistically we found that CaMK4 phosphorylates 14-3-3, releasing pro-apoptotic protein BAD which in turn binds to the antiapoptotic protein BCL-2, thereby allowing BAX, to aggregate on mitochondria and induce release of cytochrome c through mitochondrial pore formation, followed by caspase activation and apoptosis. In parallel, CaMK4 inhibits autophagy, a process needed for the renewal of damaged organelles, through the mTOR pathway, by directly phosphorylating AKT and S6 kinase.

Conclusions: We demonstrate that mice lacking CaMK4 specifically in podocytes are protected from FSGS-like disease after exposure to adriamycin. These mice also demonstrate markedly reduced proteinuria and podocytopenia. We found that apoptosis leads to cell death while autophagy is protective in FSGS. The characterization of the specific molecular events which lead to podocyte loss and glomerulosclerosis point to putative therapeutic targets and biomarkers for FSGS.

Funding: NIDDK Support. Other NIH Support - NIAID

PO1694
A Noncanonical Role for IRE1α in Podocyte Endoplasmic Reticulum (ER)-Phagy
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Background: Glomerular diseases involving podocyte (glomerular epithelial cell; GEC) injury feature endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). Inositol requiring enzyme-1α (IRE1α), a UPR transducer, mediates chaperone production and autophagy in podocytes during ER stress. Selective autophagy of the ER (ERphagy) is dependent on ER-resident adaptors (e.g. RTN3L) and is stimulated by ER stress. ER-derived coat protein complex II (COP II) vesicles may participate in the delivery of ER cargo to autophagosomes; however, regulation and importance of ERphagy in glomerular disease are not understood.

Methods: We employed mice with podocyte-specific deletion of IRE1α and littermate controls. IRE1α knockout (KO) and control GECs were produced from these mice. GECs were incubated with tunicamycin (TM) to induce ER stress.

Results: Mass spectrometry analysis of TM-stimulated control and IRE1α KO GECs showed that in addition to ER chaperones, proteins in the secretory pathway, including the COP II component Sec23B, were increased in an IRE1α-dependent manner. By immunoblotting, TM enhanced Sec23B and RTN3L expression in control, but not IRE1α KO GECs. By immunofluorescence microscopy, in control GECs, TM increased the biogenesis of LC3 and Sec23B particles, as well as colocalization of Sec23B with LC3 and RTN3L with LC3; increases were attenuated in IRE1α KO GECs. Thus, deletion of IRE1α impaired delivery of COP II vesicles and RTN3L-coated ER fragments to autophagosomes. Knockdown of Sec23B with siRNAAs reduced autophagosome formation in TM-stimulated control GECs. After blocking protein synthesis with cycloheximide, TM stimulated degradation of RTN3L in control GECs, consistent with ERphagy flux, but RTN3L degradation was impaired in IRE1α KO cells. Similarly, TM induced degradation of e3,4,5 collagen IV in control, but not IRE1α KO GECs, suggesting that collagen IV is an IRE1α-dependent ERphagy target. In adriamycin nephrosis, where IRE1α activates an adaptive UPR and autophagy, expression of Sec23B and RTN3L was increased in glomerular control, but not IRE1α KO mice.

Conclusions: During ER stress, IRE1α redirects a subset of Sec23B-positive COP II vesicles to deliver RTN3L-coated ER fragments to autophagosomes. ERphagy is a novel outcome of the IRE1α pathway in podocytes and may play a cytoprotective role in glomerular diseases.

Funding: Government Support - Non-U.S.
PO1695
ACE Inhibition Modulates Insulin-Like Growth Factor I (IGF-1) Filtration to Regulate Compensatory Kidney and Glomerular Hypertrophy

Background: Modeling suggests that preventing glomerular volume (GV) increase could serve as a therapeutic target to mitigate hypertrophy-associated progressive glomerulosclerosis (GS). We, therefore, evaluated how GV is regulated, and how Angiotensin-Converting Enzyme inhibition (ACEi) could reduce compensatory GV increase.

Methods: Uni-nephrectomized (Uni-Nx) wild-type Fischer344 rats were used to model progressive GV triggered by the single kidney state, and the effect of ACEi started either before or after Uni-Nx. Urine IGF ELISA assay, computer-assisted morphometry, single-cell, bulk transcriptomics, immunofluorescence, and human databases were analyzed.

Results: ACEi started before, but not after Uni-Nx, reduced short (Panel A) and long-term (Panel B) compensatory GV increase, and the associated 8-fold peak of urine IGF-1 post-nephrectomy (Panel C). An IGF-IR inhibitor (pirprofopophyllin) also reduced compensatory kidney hypertrophy (Panel D). Post-Uni-Nx, a decrease in both serum IGF-1 and glomerular kidney-IGF-1 transcript were noted, and IGFBP3 (the major blood IGFBP) was present in podocyte cytoplasm in the absence of detectable podocyte IGFBP3 transcript, suggesting that IGF-1 and IGF-IGFBP complexes had come from blood. A model was developed to predict how IGF-1, IGF-2, and IGF-IGFBP protein complexes would interact with the glomerular filter, and its predictions were confirmed in ERCB database. The importance of hyperfiltered IGF-1 as a driver of glomerular failure in single kidney states was further supported by human kidney allograft half-life analysis.

Conclusions: Hyperfiltered IGF-1 drives compensatory GV increase leading to long-term proteinuria and GS. Timing of ACEi in relation to Uni-Nx can reduce both IGF-1-hyperfiltration and GV increase, thereby prolonging single kidney lifespan.

Funding: NIDDK Support

PO1696
Angiotensin II Induces Oxidative Podocyte Injury via the Upregulation of Nox4
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Background: Angiotensin II (Ang II) induces glomerular and podocyte injury via systemic and local vasoconstrictive or non-hemodynamic effects including oxidative stress. The release of free radicals from podocytes may participate in the development of glomerular injury and proteinuria. We studied the pathophysiologic roles of oxidative stress in Ang II-induced podocyte apoptosis.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times and transfected by Nox4 or AT1R siRNAs or negative control scrambled siRNA for 24 h. The changes of podocyte oxidative stress and apoptosis were observed by confocal imaging, western blotting, real-time PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II increased the generation of superoxide anions and intracellular reactive oxygen species (ROS) levels but suppressed superoxide dismutase activity that was reversed by an antioxidant, probucol. Ang II also increased Nox4 protein and expression in podocytes, measured using western blotting and real-time PCR analysis that was also reversed by probucol. Nox4 suppression by small interference RNA (siRNA) reduced the oxidative stress induced by Ang II. These results suggest that Ang II induced oxidative stress via the upregulation of Nox4 protein in a transcriptional mechanism. Ang II promoted podocyte apoptosis that was reduced significantly by probucol and Nox4 siRNA. Ang II-induced podocyte apoptosis were also recovered by Ang II type 1 receptor (AT1R) siRNA.

Conclusions: Our findings suggest that Ang II induced podocyte oxidative stress and apoptosis through AT1R and Nox4. These findings suggest that Ang II promoted podocyte oxidative stress and apoptosis through AT1R and via the upregulation of Nox4, which could be reversible by Nox4 inhibition and/or antagonizing AT1R as well as antioxidants.

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

PO1697
Anillin Serves a Protective Function in a Mouse Model of HIV-Associated Nephropathy
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Background: HIV associated nephropathy (HIVAN) is characterized by a rapid progression to end stage kidney disease with limited treatment options. We previously demonstrated that mutations in the gene encoding anillin (ANLN) can cause FSGS and showed that ANLN is upregulated in the glomerulus of HIVAN patients as well as the HIVAN Tg26 mouse model. ANLN is an F-actin binding protein that affects cell proliferation and survival, two cell processes that are predicted to play a key role in the phenotype associated with HIVAN. We hypothesized that ANLN upregulation is one of the drivers of glomerular failure in HIVAN mice, therefore modulating ANLN expression may present an alternative therapeutic strategy for HIVAN.

Methods: To evaluate the therapeutic potential of reduced functional ANLN in a HIVAN mouse model, we created a mouse line using CRISPR Cas9 mediated gene editing that contains an early stop codon in the Anln gene (ANLNx). We then bred heterozygous ANLNx mice with Tg26 HIVAN mice and evaluated proteinuria and mortality over 16 weeks for each genotype. Sclerotic glomeruli from 3 mice in each group were evaluated and quantified at 16 weeks of age by pathologists blinded to genotype.

Results: There was no improvement in glomerular disease phenotype associated with the reduction of functional ANLN in the Tg26 HIVAN model. Urine albumin to creatinine ratio at 8, 12, and 16 weeks were similar between ANLNx and Tg26 heterozygotes compared to Tg26 HIVAN mice (p=0.838, 0.8063, 0.8071 for each time point). Mice heterozygous for both the ANLNx and Tg26 alleles also did not display any increase in survival compared to mice carrying only the Tg26 allele (p=0.361). Evaluation and scoring of PAS stained kidney sections by independent pathologists revealed similar levels of sclerosis between Tg26 HIVAN mice and mice heterozygous for both the ANLNx and Tg26 alleles.

Conclusions: Genetic ablation of ANLN does not improve kidney disease phenotypes in Tg26 HIVAN mice. ANLN upregulation likely represents a survival mechanism in Tg26 HIVAN mice and not a cause of injury.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Dach1 Is Essential for Maintaining Normal Podocytes
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Background: Dach1 is a transcription factor, determining cell fates in various organs. Dach1 polymorphism has been reported to be associated with nephrotic syndrome and chronic kidney diseases. We previously found that Dach1 was highly expressed in normal podocytes and rapidly disappeared after induction of podocyte injury, similarly to WT1. We aimed to elucidate the function of Dach1 in podocytes in vivo.

Methods: Because Dach1 null mice die shortly after birth, kidneys were harvested at P0 and histologically examined. To study the role of Dach1 in mature podocytes, podocyte-specific Dach1 deleted mice were generated by mating Dach1fl/fl mice with Nphs1-Cre or Nphs2-CreERTT2 mice. Eleven Nphs1-Cre/Dach1fl/fl mice were analyzed at 8-35 weeks of age. 14 Nphs2-CreERTT2/Dach1fl/fl mice were treated with tamoxifen (0.1mg/g BW/day, p.o. 5 days courses) and analyzed 7 days later.

Results: In neonatal wild-type mice, Dach1 is faintly expressed in the cap mesenchyme and increased in the renal vesicles/shaped bodies and further intensified and concentrated in mature podocytes. Dach1 is also intensely expressed in the ureteric bud. In Dach1 null mice, negative Dach1 staining was confirmed. Kidsneys of Dach1 null mice were 14.2 % smaller than those of control mice but showed normal structure. Podocytes in Dach1 null mice showed normal phenotypes in SEM and TEM with normal slit membrane, and no abnormal leakage of albumin. Immunostaining for WT1, nephrin, podocin, synaptopodin and nestin was normal. Only a small number of podocytes lacked Dach1 staining in Nphs1-Cre/Dach1fl/fl and Nphs2-CreERTT2/Dach1fl/fl mice, indicating inefficient Cre-mediated recombination. Nevertheless, all Nphs1-Cre/Dach1fl/fl exhibited abnormal albuminuria (UACR 4.7x10^6 mg/mg vs 0.06x10^6), which increased with age, and seven (63%) mice showed FSGS. Seven (50%) Nphs2-CreERTT2/Dach1fl/fl mice exhibited abnormal albuminuria, and three (21%) mice showed early sclerotic lesions. Immunostaining showed that sclerotic lesions lacked Dach1 as well as WT1, synaptopodin and nephrin. Most of Dach1 negative podocytes in non-sclerotic glomeruli had normal staining for podocyte marker proteins.

Conclusions: These results indicate that Dach1 does not determine the fate of differentiation into podocytes but is indispensable for maintaining normal integrity of mature podocytes.

Funding: Government Support - Non-U.S.

PO1700

TAZ Is Important for Structural and Functional Integrity of Podocytes
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Background: Podocyte is an important component of glomerular filtration barrier (GFB). Maintenance of integrity of slit-diaphragm(SD) structure is critical for normal kidney function. Podocytes lost most epithelial cell tight junction components except for Zonula occludens-1 and -2 (ZO-1 and ZO-2). In podocytes, ZO-1 is an important binding partner of Nephrin, and mice with podocyte-specific ZO-1 deletion showed significant growth retardation and severe proteinuria starting at 2 weeks of age, but the regulation of ZO-1 expression in podocytes are not clear. TAZ (transcriptional coactivator with PDZ-binding motif) and its paralog Yes-associated protein (YAP) are two crucial effectors of Hippo signaling pathway. Recent study has shown that podocyte-specific YAP deletion causes FSGS and progressive renal failure, but the potential role of TAZ in podocytes and chronic kidney diseases. We previously found that Dach1 was highly expressed in normal podocytes and rapidly disappeared after induction of podocyte injury, similarly to WT1. We aimed to elucidate the function of Dach1 in podocytes in vivo.

Methods: Because Dach1 null mice die shortly after birth, kidneys were harvested at P0 and histologically examined. To study the role of Dach1 in mature podocytes, podocyte-specific Dach1 deleted mice were generated by mating Dach1fl/fl mice with Nphs1-Cre or Nphs2-CreERTT2 mice. Eleven Nphs1-Cre/Dach1fl/fl mice were analyzed at 8-35 weeks of age. 14 Nphs2-CreERTT2/Dach1fl/fl mice were treated with tamoxifen (0.1mg/g BW/day, p.o. 5 days courses) and analyzed 7 days later.

Results: In neonatal wild-type mice, Dach1 is faintly expressed in the cap mesenchyme and increased in the renal vesicles/shaped bodies and further intensified and concentrated in mature podocytes. Dach1 is also intensely expressed in the ureteric bud. In Dach1 null mice, negative Dach1 staining was confirmed. Kidsneys of Dach1 null mice were 14.2 % smaller than those of control mice but showed normal structure. Podocytes in Dach1 null mice showed normal phenotypes in SEM and TEM with normal slit membrane, and no abnormal leakage of albumin. Immunostaining for WT1, nephrin, podocin, synaptopodin and nestin was normal. Only a small number of podocytes lacked Dach1 staining in Nphs1-Cre/Dach1fl/fl and Nphs2-CreERTT2/Dach1fl/fl mice, indicating inefficient Cre-mediated recombination. Nevertheless, all Nphs1-Cre/Dach1fl/fl exhibited abnormal albuminuria (UACR 4.7x10^6 mg/mg vs 0.06x10^6), which increased with age, and seven (63%) mice showed FSGS. Seven (50%) Nphs2-CreERTT2/Dach1fl/fl mice exhibited abnormal albuminuria, and three (21%) mice showed early sclerotic lesions. Immunostaining showed that sclerotic lesions lacked Dach1 as well as WT1, synaptopodin and nephrin. Most of Dach1 negative podocytes in non-sclerotic glomeruli had normal staining for podocyte marker proteins.

Conclusions: These results indicate that Dach1 does not determine the fate of differentiation into podocytes but is indispensable for maintaining normal integrity of mature podocytes.

Funding: Government Support - Non-U.S.

PO1699

Neurexin1α Containing Splice Site 4 Interacts with Nephrin and Contributes to Maintenance of the Integrity of Podocyte Slit Diaphragm
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Background: Neurexins (NRXNs) are synaptic cell adhesion molecules having essential roles in the assembly and maturation of synapses. It is known that NRXN1α contains 6 splicing sites (SSs), and multiple splicing variants were diffusely expressed in neuronal tissues. We have previously reported that NRXN1α is expressed at slit diaphragm (SD), a cell-cell junction of podocyte, and is downregulated in injured podocytes. The report also showed that NRXN1α expressed in podocytes is a unique variant containing SS1, 3, 4, and 5, which is a rare variant in neural tissues (Am J Physiol, 300:R340, 2011). However, the role of NRXN1α at SD is not well understood yet.

Methods: The interaction of NRXN1α with SD-associated molecules was analyzed by the immunoprecipitation (IP) assay. The function and structure of SD of NRXN1α KO mice were precisely analyzed.

Results: The interaction of NRXN1α with SD molecules such as nephrin and ephrin-B1 was detected by the IP assay with rat glomerular lysates. IP assay with the HEK cell expression systems showed NRXN1α containing SS4 interacted with nephrin, but NRXN1α lacking SS4 did not. The interaction between NRXN1α and nephrin was dissociated, if nephrin was phosphorylated. The interaction of NRXN1α with ephrin-B1 was not detected in the HEK system, suggesting NRXN1α interacts with ephrin-B1 via nephrin. Abnormal proteinuria (92.1 mg/day vs 23.8 mg/day, p=0.05) and clear proteinuria components (bDNA) were detected in NRXN1α KO mice at the age of 20 weeks of NRXN1α KO mice (IF score; nephrin, 2.68 vs 3.83, p=0.05; ephrin-B1, 2.68 vs 3.84, p=0.05; podocin, 2.78 vs 3.58, p=0.05), although these alterations were not detected at the age of 10 weeks. The phenotypes of the KO mice suggest NRXN1α does not play a major role for formation of SD but contributes to the maintenance of the integrity of SD at an elderly age.

Conclusions: Neurexin1α containing SS4 interacts with nephrin, and is a novel SD component. NRXN1α contributes to maintenance of the function and the molecular integrity of SD. It is conceivable that downregulation of NRXN1α participates in the development of podocyte injury onset at an elderly age.

Funding: Government Support - Non-U.S.

PO1702

Possible Role of the Cytosolic RNase Inhibitor in Maintaining the Integrity of the Glomerular Filtration Barrier
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Background: The ribonuclease inhibitor (RI) is a cytoplasmic protein encoded by the RNHI1 gene. The RI forms a tight non-covalent bond with members of the RNaseA superfamily and therefore it’s considered that its main function is to act as a sentinel for dysregulated RNases. The ratio of RI to substrate has also been shown to vary according to the proliferative and metabolic status of the cell suggesting that the balance in the protein-protein interactions between the RI and its substrates plays a role in maintaining cell homeostasis by impacting processes such as protein synthesis and various signaling pathways. However, the entirety of the biological roles fulfilled by the RI are yet to be described.

Methods: Immunofluorescence staining of human kidney tissue and protein detection by western blot from samples of immortalized podocytes were carried out to confirm the presence of the RI in glomerular cells. As an initial injury model, podocytes were treated with PAN to determine if changes in RI expression occur as a response. RNHI1 inhibition was performed in a transgenic zebrafish line that allows for the detection of proteinuria via a GFP-tagged protein in the circulation. At 90hpf the severity of the edema phenotype and the fluorescence levels were recorded.

Results: Our preliminary data shows that the RI is present in human podocytes both in vitro and in vivo, as its expression domain coincides with glomerular cells labelled with synaptopodin. Additionally, the RI is present in cultured podocytes both before and after the temperature shift used to induce quiescence, and it appears to increase after differentiation. There is also expression modulation of RNHI1 in response to PAN treatment of podocytes. In our zebrafish model, RNHI1 knockdown resulted in up to a 40% increase in mild to severe edema and over 30% decrease in fluorescence suggesting that a reduction in RI might compromise the filtration barrier enough to lead to proteinuria.

Conclusions: Taken together our initial data show a promising avenue for research where the balance between members of the RNaseA superfamily and their cytoplasmic inhibitor may represent a powerful mechanism that allows the cells to modulate the proliferative response to stimuli. An imbalance in this relationship might ultimately affect the integrity of the cells in the kidney.

Funding: Government Support - Non-U.S.
PO1703

Atypical Caspase 3-Dependent Death in Podocytes
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Background: Apoptosis of podocytes has been widely reported in many in vitro studies, but definitive apoptosis has never been documented in vivo podocytes. To elucidate this discrepancy, we analyzed dying process in podocytes in vitro and in vivo.

Methods: Primary mouse podocytes were transiently transfected with ICD25 and EGFP expression plasmids and treated with a ICD25-targeting immunotoxin, LMB2 (1nM), and observed 1 day later. In some experiments, the cultured podocytes were transfected with Bak1 or Bax siRNA before treatment with LMB2. In in vivo experiments, podocyte injury was induced by injecting LMB2 (1.25ng/gBW) into NEP25 mice, which express ICD25 in podocytes, and analyzed 7 days later.

Results: In in vitro studies, administration of LMB2 caused loss of co-introduced EGFP in 56.8±13.6%, incorporation of propidium iodide in 15.6±2.5%, activation of caspase 3 (Casp3) in 19.6±2.6% and TUNEL staining in 4.5±1.3% without significant increase in LDH activity in the culture medium. These phenomena were not observed in cells without ICD25 or without LMB2. Ac-DEVD-CHO (10uM), a Casp3 inhibitor, attenuated the loss of EGFP by 38.2%. Inhibition of Bak1 and Bax using siRNAs attenuated EGFP loss by 77.6% and 28.4%, respectively. These indicate that LMB2 induced the typical Casp3 dependent intrinsic apoptosis in podocytes in vitro. In in vivo studies, kidneys of NEP25 mice contained podocytes positive for cleaved (c) Casp3 and those for ClaminA, a product of Casp3, but no TUNEL+ podocytes. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. The urinary sediments contained podocalyxin-positive podocytes (2.5±0.3%). Among these, 39.1±3.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. To evaluate the effect of glomerular filtration, NEP25 mice were similarly injected with LMB2 and subjected to UUO 1 day before sacrifice. The obstructed kidney contained significantly more cLaminA+ podocytes than the contralateral kidney. In addition, detaching podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: Thus, due to physical force of glomerular filtration, podocytes doomed to Casp3 dependent death are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. This accounts for the absence of podocyte apoptosis in vivo.

PO1705

Glomerular Endothelial Cell-Derived MicroRNA-192 Regulates Podocyte Nephrinectin in Membranous Glomerulonephritis

Background: Autoantibodies binding to podocyte antigens cause idiopathic membranous glomerulonephritis (mGN). It remains elusive how autoantibodies reach the subepithelial space because the glomerular filtration barrier (GBF) is normally size-selective and impermeable for antibodies.

Methods: Kidney biopsies from patients with mGN, cell culture, zebrafish and mice models were used to investigate the role of nephrinectin (NPNT) regulating microRNAs (miRs) for the GBF.

Results: Glomerular endothelial cell (GEC)-derived miR-192-5p and podocyte-derived miR-378a-3p are upregulated in glomeruli of patients with mGN whereas NPNT expression is reduced. Overexpression miR-192-5p as well as morpholino-mediated mnt knockdown induced edema, proteinuria and podocyte effacement similar to podocyte-derived miR-378a-3p in zebrafish. Moreover, structural changes of the glomerular basement membrane (GBM) with increased lucidity, slicing and lamellation especially of the lamina rara interna similar to ultrastructural findings seen in advanced stages of iMGN were found (Fig. 1). IgG size nanoparticles accumulated in lucidity areas of the lamina rara interna and lamina densa of the GBM in mnt knockdown zebrafish models. Loss of slit diaphragm proteins and severe structural impairment of the GBM were further confirmed in podocyte-specific Npnt knockout mice. GECs downregulate podocyte Nptnt by secretion of miR-192-5p containing exosomes in a paracrine manner.

Conclusions: Podocyte Nptnt is important for proper GBF function and GBM structure and is regulated by GEC-derived miR-192-5p and podocyte-derived miR-378a-3p. We hypothesize that loss of Nptnt in the GBM is part of the pathophysiology of mGN and enables subepithelial immune complex deposition in iMGN.

PO1704

Mice Deficient in Aminopeptidase A Have Worse Glomerular Injury in Response to Chronic Renal Mass Reduction
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Background: Aminopeptidase A (APA) is a membrane-bound metalloprotease expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding suggests that APA also plays a role in the maintenance of glomerular structure. We have shown in vivo experiments, kidneys of NEP25 mice contained podocytes positive for cleaved (c) Casp3 and those for ClaminA, a product of Casp3, but no TUNEL+ podocytes. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. The urinary sediments contained podocalyxin-positive podocytes (2.5±0.3%). Among these, 39.1±3.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. To evaluate the effect of glomerular filtration, NEP25 mice were similarly injected with LMB2 and subjected to UUO 1 day before sacrifice. The obstructed kidney contained significantly more cLaminA+ podocytes than the contralateral kidney. In addition, detaching podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: Thus, due to physical force of glomerular filtration, podocytes doomed to Casp3 dependent death are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. This accounts for the absence of podocyte apoptosis in vivo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1706

Identification of the Mechanism Underlying the Toxicity of Systemically Administered miR-145-5p on Podocytes Based on Podocyte Essential Genes

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Background: MicroRNAs are emerging as effective therapeutic agents. MiR-145-5p dysregulation has been shown to be involved in kidney injury. To determine whether supplement of miR-145-5p would alleviate kidney injury in mouse models, we first tested the miR-145-5p enriched extracellular vesicles (miR-145-5p EVs) sample for toxicity or side effects on healthy control mice.

Methods: miR-145-5p EVs were injected to mice intravenously every day for a total of 6 days. A group of mice were simultaneously injected with miR-145-5p inhibitor using TransIT®-EE Delivery Solution. Cultured cells were transfected with RNAiMAX or Fugene.

Results: miR-145-5p EVs resulted in proteinuria and podocyte foot process effacement in normal control mice, and this effect was abolished by miR-145-5p inhibitor. We demonstrated that systemically administered miRNA can enter podocytes. miR-145-5p EVs could enter cultured podocytes and cause F-actin loss. miR-145-5p mimic caused a similar reduction of F-actin in the cells. We speculated that miR-145-5p is toxic to podocytes because it is not normally expressed in podocytes and exogenous miR-145-5p can effectively target genes essential for podocytes. By using the concept that genes commonly expressed in all individual podocytes are likely podocyte essential genes, we predicted podocyte essential genes when expression cutoff was set to > 0.1 RPMK. We found that 32 of them are predicted to be targeted by miR-145-5p. Functional annotation of the 32 genes revealed small GTPase mediated signal transduction as the top function. Among genes associated with the small GTPases pathway, Arhgap24 is known to control the Rac1 GTPase activity. We performed APATrap and JunctionSeq bioinformatics analyses software, and we found miR-145-5p significantly repressed Arhgap24 expression in podocytes in vivo and in vitro. miR-145-5p increased activity of both Rac1 and Cdc42.

Conclusions: MiR-145-5p induced podocyte injury through targeting podocyte essential genes associated with small GTPase mediated pathway. Our study provides a novel approach to investigate how a miRNA affects a given cell type, allowing not only identification of the molecular mechanism underlying an observed side effect of a miRNA drug but also prediction of miRNA drug toxicity on various cell types.

Funding: Government Support - Non-U.S.

PO1707

Glomerular miRNAs Are Alternatively Spliced and Polyadenylated During Podocyte Injury in Animal Models of Nephrotic Syndrome

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Background: Glomerular disease, often manifesting as nephrotic syndrome (NS) with high proteinuria, is characterized by podocyte loss and injury. Furthermore, alternative miRNA processing, such as alternative splicing (AS) and alternative polyadenylation (APA) play important roles in physiology, development, and disease; however, there is very limited knowledge on their roles in glomerular disease. We hypothesized that AS and APA events of glomerular RNAs is associated with podocyte injury and proteinuria in NS.

Methods: Glomerular damage characterized by proteinuria was induced by purmorphamin aminonucleoside (PAN) or adriamycin (ADR) to mimic human minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), respectively. Urine and serum chemistries, kidney histology and glomerular RNA-seq analyses were performed. APATrap and JunctionSeq bioinformatics analyses software were used to detect APA and AS glomerular events. Correlation of differentially expressed genes (DEGs) was performed with known glomerular disease genes and polyadenylation and splicing factors.

Results: Robust proteinuria was induced in both PAN-MCD and ADR-FSGS models, accompanied by hyperaluminaemia, hypercholesterolaemia and histological alterations in the kidneys (protein casts and podocyte hypertrophy). Out of 13,265 genes, MCD model resulted in 1033 and FSGS model in 1308 glomerular DEGs with abs(log2FC)>1 and p<.05. Of 80 analyzed genes with established roles in glomerular disease, 30 were altered in both MCD and FSGS. Significant APA was identified in 71 and 746 genes in MCD and FSGS, respectively. Similarly, 21 were altered in MCD and 24 in FSGS. Significant AS was identified in 136 and 1875 genes in MCD and FSGS models, respectively. In accordance, of 50 splicing factors analyzed, 3 were altered in MCD and 5 in FSGS. Specifically, the identified APA and AS events affected genes of the slit diaphragm complex such as Neph1, Neph2, and Tjp1, which are critical determinants of podocyte structure and function.

Conclusions: Association of global glomerular miRNA alteration due to AS and APA with podocyte and glomerular injury is a newly recognized phenomenon, with potential implications for therapy and molecular understanding of the disease.

Funding: Other NIH Support - NIH Clinical and Translational Science Award to The Ohio State University (Award Number UL1TR002733 from the National Center for Advancing Translational Sciences), Private Foundation Support

PO1708

Continuous Non-Mutagenic DNA Damage in Podocytes Activates Inflammatory Response and May Accelerate Kidney Aging

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Background: Podocytes are suggested to contribute to kidney aging because of their terminally differentiated features. We have previously reported the association of KAT5-mediated DNA damage repair with altered DNA methylation in podocytes (Cell Rep 2019). However, the role of podocyte DNA damage itself on DNA methylation changes and kidney aging has remained to be adequately elucidated.

Methods: To investigate the significance of DNA double-strand breaks (DSBs) in podocytes, we generated podocyte-specific I-Ppol knockout mice (podocin-Cre ROSA26-STOP- I-Ppol) . I-Ppol is a homing endonuclease which causes non-mutagenic DSBs. RNA-seq and MeDIP-seq analysis were performed using isolated podocytes in I-Ppol mice and wildtype controls.

Results: I-Ppol mice showed severe albuminuria (WT 43±3.4 mg/gCr, I-Ppol 2224±7.3 mg/gCr, p<0.01) with diffuse foot process effacement in podocytes but glomerulosclerosis and interstitial fibrosis were not observed at 12 weeks of age. Interestingly, infiltration of CD11b-positive cells was shown in I-Ppol podocytes, which is a similar finding in 2-year-old aged mice. The aged mice showed increased DNA damage and DNA methylation. In I-Ppol mice, rapid deterioration of renal function with glomerulosclerosis and tubulointerstitial fibrosis developed around the age of 20 weeks. RNA-seq analysis revealed that inflammatory-related genes were upregulated in podocytes of I-Ppol mice. Senescence-associated secretory phenotype (SASP)-related gene expression was also increased. MeDIP-seq analysis revealed that 5219 differentially methylated regions (DMRs) were identified in I-Ppol mice compared with controls. Interestingly, there was no significant correlation between the distance from the I-Ppol cutting site and DMRs. DNA methylation was increased in genes containing I-Ppol cutting sites or podocyte epithelial genes such as neprhin and podocin, whereas it was decreased in inflammatory related genes, suggesting gene-specific DNA methylation changes following DNA damage.

Conclusions: The phenotype of the I-Ppol mice may reflect one aspect of accelerated kidney aging. Repeated DNA damage repair in podocytes may cause altered DNA methylation independent of primary DNA damaged sites with promoted inflammation and podocyte morphological changes.

PO1709

Deletion of MCP-1 in Podocytes Does Not Protect Against Glomerular Injury

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Background: Over the past three decades, the global burden of chronic kidney disease (CKD) has nearly doubled straining healthcare budgets. Understanding the role of podocytes in the pathophysiology of proteinuric disease is important for development of novel treatments. Prior studies implicate monocyte chemotractant protein-1 (MCP-1) in podocyte injury, but the source of MCP-1 has not been definitely identified. Both MCP-1 and its cognate receptor, CCR2, are expressed in podocytes. Therefore, using podocyte-specific MCP-1 knockout mice (PODO-MCP-1-/-), we evaluated whether autocrine MCP-1 signaling by podocytes contributes to proteinuric CKD.

Methods: PODO-MCP-1-/- mice were generated by crossing MCP-1 flexed mice with mice harboring Cre recombinase under the control of the podocin promotor. Knockout mice and wild-type littermates were subjected to angiotensin II by osmotic minipumps (Ang II; 1.5mg/kg/day) for 28 days. Weekly spot urines were collected, assessed with ELISA for albuminuria, and results normalized to urinary creatinine. After 28 days, kidneys were harvested and histologic, immunofluorescent, immunoblot, and quantitative PCR analyses were performed. Results are reported as mean ± S.E.M. Threshold for significance was P<.05.

Results: There were no baseline differences in bodyweight, histology, and urinary albumin levels between the two groups. Following 28 days of Ang II infusion, histologic analysis revealed renal pathology particularly glomerulosclerosis. There were no differences in bodyweight, albuminuria, renal function, expression of nephrin and WT1, and number of podocytes. Ccr2 gene expression also revealed no significant difference.

Conclusions: Our results demonstrate that podocyte-specific MCP-1 production is not a major contributor to Ang II-induced glomerular injury as demonstrated by lack of protection in the podocyte-specific MCP-1 knockout mice. Future studies will evaluate other sources of MCP-1 that may impact disease.

Funding: NIDDK Support, Private Foundation Support
PO1710

Delayed Treatment with a Novel Highly Selective Small-Molecule Agonist of MC5R Attenuates Podocyte Injury and Proteinuria in Puromycin Aminonucleoside Nephrosis

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Background: Clinical studies indicate that the melanocortin peptide ACTH is effective in inducing remission of nephrotic glomerulopathies like MCD and FSGS, even those resistant to steroids, suggesting that a steroid-independent melanocortinergic mechanism might contribute. However, the type of melanocortin receptor (MCR) that conveys this beneficial effect as well as the underlying mechanisms remains controversial. Recently, burgeoning evidence suggests that MC5R is likely involved in glomerular pathobiology. This study aims to test the effectiveness of a novel highly selective MC5R agonist (MC5RA) in puromycin aminonucleoside (PAN) nephrosis.

Methods: MC5RA was generated by N-terminal modification of the melanocortin core tetrapeptide His-D-β-Arg-Trp-NH₂ with an aromatic group, resulting in a triphenylpropionyl melanocortin analog with a 100-fold selective agonistic activity on MC5R. Rats were injured with a tail vein injection of PAN, and 5 days later, were randomized to daily MC5R or vehicle treatment.

Results: Upon PAN injury, rats developed heavy proteinuria on day 5, entailing an established nphrotic glomerulopathy. Following vehicle treatment, proteinuria continued to progress on day 14 and was sustained till day 21, accompanied by evident histologic signs of podocyteopathy, marked by ultrastructural lesions of glomeruli, including extensive effacement of podocyte foot processes and podocyte microvillus transformation, and concomitant with loss of podocyte homeostatic markers, such as synaptopodin and nephrin, and de novo expression of podocyte injury marker desmin. Rescue treatment with MC5SA significantly attenuated urine albumin excretion and mitigated the loss of podocyte markers proteins, resulting in improved podocyte ultrastructural changes. In vitro in cultured podocytes, MC5RA prevented the PAN-induced disruption of actin cytoskeleton integrity and apoptosis. Mechanistically, MC5RA treatment reinstated inhibitory pharmacology and thus averted hyperactivity of GSK3β, a critical point of multiple podotypathic pathways, in PAN-injured podocytes in vitro and in vivo.

Conclusions: Pharmacologic targeting of MC5R by using the highly selective small-molecule agonist is likely a promising and feasible therapeutic strategy to improve proteinuria and podocyte injury in glomerular disease.

Funding: NIDDK Support

PO1711

Tadalafil, a PDE5 inhibitor, Exhibits Renoprotective Effects Preventing Podocyte Damage in an Adriamycin-Induced Nephrotic Syndrome Model

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Background: Phosphodiesterase (PDE)-5 inhibitor is reportedly a renoprotective compound. Although PDE5 expression is confirmed in the glomeruli, its relationship with renal dysfunction remains elusive. We have previously investigated the renoprotective effects of tadalafil in a CKD model (Tomita N, et al. Physiol Rep. 2020), suggesting that such an effect would be related to podocyte damage attenuation. In this study, we investigated how tadalafil, a PDE5 inhibitor, could affect a rat nephrotic syndrome model.

Methods: Wistar ST rats were established as nephrotic syndrome models by administrating adriamycin (ADR) injection. The animals were divided into 3 groups: control (n = 6), ADR (n = 5), and ADR + tadalafil (n = 5). Tadalafil was administered 10 mg/kg daily. After 2 weeks of treatment, the urinary protein and serum albumin levels were evaluated, and the kidney tissue was harvested. WT1-positive cells were identified as podocytes by WT1 immunostaining. Moreover, human renal glomerular epithelial cell damage was induced in vitro by ADR supplementation. After 24 h of ADR treatment with or without tadalafil, cell viability was determined using CCK-8.

Results: The ADR injection induced high urinary protein and low serum albumin levels. Two weeks of tadalafil treatment attenuated proteinuria compared to the ADR group (P < 0.01). ADR reduced the WT1-positive cell number and the tadalafil treatment prevented the reduction (P < 0.05). Moreover, the ADR treatment resulted in reduced cell viability in vitro. The tadalafil treatment improved cell viability compared to the ADR treatment only (P < 0.05).

Conclusions: This study suggests that the treatment with tadalafil, a PDE5 inhibitor, could effectively prevent podocyte damage in the case of nephrotic syndrome.

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PO1712

Targeting mTOR Signaling Improved Kidney Function in APOL1 Risk Variant Mice with Chronic Exposure to Inflammatory Stimuli

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Background: Inheriting two copies of APOL1 risk variants significantly increases the likelihood of developing chronic kidney disease in African Americans. Many different types of disease have been proposed using cell-based model systems. Here we try to understand risk variant pathophysiolog by using a transgenic mouse model.

Methods: Transgenic mice with a single copy of human APOL1 G0 and G2 were generated using bacterial artificial chromosome (BAC) on a FVB background. Mice were injected with interferon gamma (IFN-γ) plasmid via hydrodynamic tail vein injections to induce APOL1 expression. Since mTOR activation has been frequently observed in podocytes during FSGS, we blocked the pathway using rapamycin to see if it could improve disease outcomes. Mice were injected with 2mg/kg of rapamycin every other day (3 days/week, intraperitoneally) for a total of 2 weeks. Paraffin embedded tissue sections were used for immunohistochemistry and Periodic acid–Schiff (PAS) staining. Glomerular isolations were performed using Dynabeads. APOL1 oligomerization was assessed using blue native PAGE.

Results: 7 Days after IFN-γ plasmid injection, the podocytes of G2 mice stained positive for phospo-S6 ribosomal protein indicating mTOR activation accompanied by proteinuria. Blocking mTOR activation using rapamycin reversed ribosomal protein S6 phosphorylation, reduced proteinuria, and improved tissue histology as seen by PAS staining. We hypothesized that rapamycin might be activating autophagy and clearing APOL1 oligomers, but found no evidence for this mechanism of rescue. Instead, we were able to replicate the rescue we had observed with rapamycin using a cell cycle inhibitor, suggesting that rapamycin might be rescuing G2 phenotype by inhibiting podocyte cell entry downstream of risk variant mediated injury.

Conclusions: Persistent expression of APOL1 risk variants pushes podocytes into cell cycle entry. Inhibiting mTOR signaling and subsequent cell cycle entry alleviated injury.

Funding: Other NIH Support - NIMHD, Other U.S. Government Support

PO1713

Plin5 Deficiency in Podocyte Negatively Affects the Communication Between Lipid Droplets and Mitochondria in Alport Syndrome

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Background: Alport Syndrome (AS) is a hereditary disease caused by mutations in collagen type IV. We and others have demonstrated pathogenic renal lipid droplets (LD) and triglyceride (TG) accumulation in experimental AS (Col4a3K/O mice). Excessive FA accumulation resulting from increased expression of TG is a major contributor to cell lipotoxicity. Perilipin 5 (PLIN5) is an LD-related protein that plays a critical role in regulating TG lipase activity and the interactions between LD and mitochondria, where it protects mitochondria from excessive exposure to FA. Here we test the hypothesis that PLIN5 deficiency, when expressed in podocytes and that PLIN5 deficiency in AS causes extracellular TG breakdown and the loss of LD-mitochondrial contact, thus contributing to kidney failure.

Methods: In vitro, Immortalized AS podocytes and WT podocytes were established and characterized in our laboratory by breeding the Col4a3K/O mice (Jackson Laboratory) to H-2kb-tsA58 transgenic mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in AS podocytes and kidney cortex in AS mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. LD-Mitochondrial contact was determined by TEM analysis.

Results: PLIN5 deficiency was observed in the kidney cortex of Col4a3K/O mice when compared to controls (p < 0.001). We demonstrate that PLIN5 is expressed in podocytes, and the expression of PLIN5 is significantly decreased in AS podocytes compared to WT podocytes (p < 0.001). AS podocytes also showed significantly increased rates of TG lipolysis (p < 0.05), intracellular free fatty acids (p < 0.05) and apoptosis (p < 0.01) when compared to WT podocytes. AS podocytes had reduced number of LD-mitochondrial contacts (p < 0.05), implying that and apoptosis. Moreover, Ezetimibe, which restored LD-Mitochondrial contact in vitro (p < 0.05) and improved kidney function in vivo, was found to restore PLIN5 expression in vitro and in vivo (p < 0.05).

Conclusions: Our study suggests that podocyte PLIN5 deficiency may cause podocyte injury in AS through excessive TG lipolysis and inefficient FA transfer from LD to Mitochondria, leading to mitochondrial dysfunction and contributing to disease progression.
POI1714

UCP2 Regulates Mitochondrial Dynamics and Podocyte Injury by OMA1-Dependent Proteolytic Processing of OPA1
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Background: Podocyte injury and loss are pivotal events in the progression of glomerular diseases, such as diabetic kidney disease (DKD) and focal segmental glomerulosclerosis (FSGS). Disordered mitochondrial dynamics leads to mitochondrial dysfunction, which is extensively involved in podocyte injury. The mitochondrial inner membrane uncoupling protein, UCP2, is involved in the regulation of mitochondrial dynamics, but the specific mechanism is unknown.

Methods: The function and structure of podocyte were detected by electron microscopy, immunofluorescence, and primary urinary albinosis. A Seahorse Bioscience XF24 Extracellular Flux Analyzer was used to measure dissolved oxygen in culture medium around adherent cells. Mitochondrial membrane potential was detected using TMRM dye. The content of ATP in cells of each well was determined with an ATP Assay Kit.

Results: We reported that the mitochondrial inner membrane UCP2 expression in podocyte was correlated with proteinuria level in patients. Mice with podocyte-specific Ucp2 deficiency developed podocytopathy with proteinuria with aging. Furthermore, those mice exhibited increased proteinuria in experimental models evoked by diabetes or adriamycin. Our findings suggest that UCP2 mediates mitochondrial dysfunction by regulating mitochondrial dynamic balance. Ucp2 deleted podocyte exhibited increased mitochondrial fission and deficient in ATP production. Mechanistically, opacity protein 1 (OPA1), a key protein in fusion of mitochondrial inner membrane, was regulated by UCP2. Ucp2 deficiency promoted proteolysis of OPA1 by activation OMA1 which belongs to mitochondrial inner membrane zinc metalloproteinase. These findings demonstrate the role of UCP2 in mitochondrial dynamics in podocyte and provide new insights into pathogenesis associated with podocyte injury and proteinuria.

Conclusions: Our findings suggest that UCP2 protects mitochondrial dynamics balance by OMA1-dependent proteolytic processing of OPA1.

Funding: Government Support - Non-U.S.

POI1715

L-WNK1 Inhibition Protects from Glomerular Injury in Mice
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Background: The With no lysine (K) kinase L-WNK1 plays a key role in the maintenance of cellular homeostasis in response to variations in osmolarity, intracellular chloride concentration or cell volume. We have shown that L-WNK1 activation in the glomerulus, its predominant site of expression within the kidney.

Methods: The function and structure of podocyte were detected by electron microscopy, immunofluorescence, and primary urinary albinosis. A Seahorse Bioscience XF24 Extracellular Flux Analyzer was used to measure dissolved oxygen in culture medium around adherent cells. Mitochondrial membrane potential was detected using TMRM dye. The content of ATP in cells of each well was determined with an ATP Assay Kit.

Results: We reported that the mitochondrial inner membrane UCP2 expression in podocyte was correlated with proteinuria level in patients. Mice with podocyte-specific Ucp2 deficiency developed podocytopathy with proteinuria with aging. Furthermore, those mice exhibited increased proteinuria in experimental models evoked by diabetes or adriamycin. Our findings suggest that UCP2 mediates mitochondrial dysfunction by regulating mitochondrial dynamic balance. Ucp2 deleted podocyte exhibited increased mitochondrial fission and deficient in ATP production. Mechanistically, opacity protein 1 (OPA1), a key protein in fusion of mitochondrial inner membrane, was regulated by UCP2. Ucp2 deficiency promoted proteolysis of OPA1 by activation OMA1 which belongs to mitochondrial inner membrane zinc metalloproteinase. These findings demonstrate the role of UCP2 in mitochondrial dynamics in podocyte and provide new insights into pathogenesis associated with podocyte injury and proteinuria.

Conclusions: Our findings suggest that UCP2 protects mitochondrial dynamics balance by OMA1-dependent proteolytic processing of OPA1.

Funding: Government Support - Non-U.S.

POI1716

Protective Role of the Epithelial STAT5 Pathway in Kidney Injury
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Background: During kidney diseases, diverse tissue-specific pathways can regulate kidney injury and prognosis. Thus, therapeutic targeting of these pathways could improve the management and prognosis of chronic kidney diseases. The Janus Kinase/ Signal Transducer and Activator of Transcription (JAK/STAT) pathway, classically described in immune cells, has been recently described in intrinsic kidney cells.

Methods: We 1) analyzed STAT5 activation in kidney biopsies from patients with focal segmental glomerulosclerosis (FSGS) and acute tubular injury (ATI), 2) used experimental models of glomerular and tubular injury in mice with podocyte- or tubular-specific STAT5 deficiency, 3) studied transcriptional modifications related to STAT5 deletion in human kidney epithelial cells, 4) explored interleukin-15 mediated STAT5 activation in podocytes and glomerular injury.

Results: Here, we show, for the first time, that STAT5 is activated in both human podocytes (Figure 1A) and tubular cells in FSGS and ATI, respectively. Additionally, STAT5 deficiency in either glomerular or tubular epithelium aggravates the functional and structural alterations in a range of experimental models of glomerular (Figure 1B) or tubular disease. STAT5 deficiency in kidney epithelial cells resulted in dysregulation of multiple metabolic pathways, including glycolysis and oxidative phosphorylation (Figure 1C). Interleukin 15 (IL-15), a classical activator of STAT5 in immune cells, increases STAT5 phosphorylation in human podocytes and alleviates glomerular injury in vivo (Figure 1D) by activating anti-apoptotic pathways.

Conclusions: In conclusion, activating renal epithelial STAT5 represents a new therapeutic avenue with the potential for a range of beneficial effects in kidney diseases.

POI1717

Shiga Toxin Targets the Podocyte in Haemolytic Uraemic Syndrome (HUS) Resulting in Glomerular Endothelial Cell Complement Dysregulation
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Background: Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy (TMA) that has a predilection to present in the kidney. It is a triad of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. In 90% of cases, HUS follows gastroenteritis secondary to enterohemorrhagic infection with Shiga toxin (Stx) producing bacteria such as Escherichia coli. Stx HUS is the leading cause of acute kidney injury in children with a mortality of 5%. However, the precise pathophysiological mechanisms following Stx infection leading to TMA remain poorly understood. Here we show that the podocyte is a key initiator in Shiga toxin HUS, which could explain why the glomerulus is the prime target of systemic Shiga toxin driven infection.

Methods: To demonstrate that the podocyte Shiga toxin receptor (Gb3) is sufficient to trigger the development of HUS, we used conditional gene targeting to engineer human Gb3 expression specifically in the podocytes of adult mice.

Results: Following intraperitoneal Shiga toxin challenge, these mice developed thrombocytopenia, haemolytic anaemia and uremia (Figure 1) with evidence of glomerular TMA on histology. Interrogation of this model revealed evidence of glomerular endothelial cell complement activation, with loss of local complement factor H protection. Furthermore, C5 inhibition was found to rescue the Shiga toxin HUS phenotype.

Conclusions: Together, these observations provide compelling evidence for the importance of podocyte-glomerular endothelial cell cross-talk within the kidney in the development of Shiga toxin associated HUS and suggest a possible therapeutic role for complement inhibition in patients with this devastating disease.

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533
PO1718

Nephronectin Expression Is Controlled by the Non-Canonical TGF-β Pathway in Podocytes

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Background: Within the glomerulus, podocytes, glomerular endothelial cells (GEC) and the glomerular basement membrane (GBM) build the glomerular filtration barrier. Extracellular matrix (ECM) of the GBM is mainly composed of proteins synthesized by GECs and podocytes. Our interest focuses on nphronectin (NPNT), an ECM protein mainly produced by podocytes. Recently, it has been described that NPNT expression patterns vary in different glomerular diseases. For example, in focal segmental glomerulosclerosis (FSGS) and membranous glomerulonephropy (MGN) NPNT expression was decreased compared to healthy controls, while it was increased in diabetic nephropathy (DN). In addition, transforming growth factor beta (TGFβ) is able to down-regulate NPNT on both mRNA and protein level. Our aim is to further analyze this TGFβ-mediated regulation of NPNT in human podocytes.

Methods: Immunolized human podocytes were differentiated for 10 to 12 days at 37°C and pre-incubated with inhibitors for components of the canonical and the non-canonical TGFβ signaling pathway with subsequent culture in the presence or absence of TGFβ. We used cell culture supernatants for ELISA, as well as cell lysates for qPCR and western blot analyses.

Results: While treating differentiated immortalized human podocytes with TGFβ decreased NPNT on both mRNA and protein level, we observed that inhibition of single components of the TGFβ pathway did not alter NPNT mRNA expression and exontr. On protein level, we noted no change after blockade of either Smad2 or Smad3 under baseline conditions. However, TGFβ was still able to decrease NPNT expression when canonical pathway components were inhibited, suggesting a minor role for this pathway in NPNT regulation via TGFβ. If single components of the non-canonical pathway were blocked, we observed an increase in NPNT protein expression, which was not further altered by TGFβ addition.

Conclusions: Taken together, our data suggest that in podocytes NPNT expression is fine-tuned via the non-canonical TGFβ pathway with additional regulation on the post-translational level.

Funding: Government Support - Non-U.S.

PO1719

Podocyte Damage in Chimeric Kidney Organoids

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Background: We previously found that when a portion of podocytes are injured, other podocytes are secondarily injured in a mouse model, which may underlie the relentless progression of chronic renal failure. In the present study, we tested whether this phenomenon is observed in kidney organoids.

Methods: Nephrin organoid cells (NPCs) were established by culture-dependent purification (CDP) method from 12.5-dpc NEP25 and RiboTag mouse kidneys (Cell Stem Cell, 2016, 19, 516-29). Podocytes of NEP25 mice express hCD25 and can be injured by hCD25-targeted immunotoxin, LMB2. Podocytes of RiboTag mice express hemagglutinin (HA)-tagged ribosomal protein. Kidney organoids were generated by transient stimulation with FGFI and CHIR99021 of NPC aggregates and subsequent 8-day culture. On day 8, LMB2 (20 nM) was added to induce injury in hCD25+ podocytes.

Results: We confirmed that podocytes in both organoids are stained for nephrin, podocin and WT1. Podocytes derived from NEP25 NPC expressed hCD25 and were injured by LMB2, and those from RiboTag NPC expressed HA and were resistant to LMB2. When two types of NPCs were mixed at 1:1 ratio, organoids showed a chimeric pattern containing hCD25+ and HA+ podocytes (Fig). 2 days after LMB2 treatment, hCD25 staining completely disappeared accompanied by cleaved (c)- lamin A staining, a cell death marker. HA staining was retained, but WT1 was diminished and podocin disappeared (Fig 2). Occasionally, c-lamin A was positive in HA+ cells. RNA of Ribotec podocytes can be obtained by immunoprecipitation with anti-hemagglutinin (HA) antibody. Q-PCR revealed that Nphs1 (0.31), Nphs2 (0.04), Wt1 (0.37) were decreased to the indicated fold by LMB2 and that Gadd45β was increased to 4.82-fold.

Conclusions: Thus, podocyte damage damages podocytes in kidney organoids that lack glomerular filtration.

Funding: Government Support - Non-U.S.
PO1721

Podocyte-Derived RARRES1 Aggravates Kidney Disease Progression by Inducing Both Glomerular and Tubular Injury

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Background: Our previous study demonstrated that the expression of retinoic acid receptor responder protein 1 (RARRES1) increases in glomeruli of patients with diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS). The glomerular expression of RARRES1 also correlates with eGFR slope and predicts glomerular disease progression. Single-cell RNA-sequencing of the kidney showed that RARRES1 was expressed mostly in podocytes within the kidney. Mechanistically, WT-RARRES1 is cleaved into a soluble form which subsequently induces podocyte apoptosis whereas mutant RARRES1 with cleavage defect failed to induce podocyte apoptosis in vitro. Here, we further determined whether increased expression of WT-RARRES1 in the podocytes aggravated progression of glomerular disease.

Methods: Mice with podocyte-specific overexpression of human WT-RARRES1 or mutant RARRES1 with cleavage defect were generated and then subjected to aging, adriamycin (ADR) administration or streptozotocin (STZ) injection. To identify the role of podocyte-derived soluble RARRES1 in tubular cells, HK2 cells were treated with soluble RARRES1 obtained from podocyte supernatants.

Results: In vivo, podocyte-specific overexpression of WT-RARRES1 resulted in severe proteinuria and marked glomerular cell injury in mice with aging, adriamycin-induced nephropathy, or STZ-induced diabetic nephropathy as compared to the control mice with overexpression of mutant RARRES1. Interestingly, tubular vacuolation and interstitial injury were also observed in these mice with podocyte-specific overexpression of RARRES1. In addition, we showed that soluble RARRES1 collected from podocyte supernatants was endocytosed in HK2 cells to induce cellular injury. Similarly, cleaved form of human RARRES1 in the mice with podocyte-specific human RARRES1 overexpression was found in the tubular compartments, indicating that soluble RARRES1 generated from podocytes may act on tubular cells through glomerulotubule crosstalk.

Conclusions: Our study suggests that RARRES1 is a risk gene for glomerular disease progression through its direct effects in podocytes as well as indirect effects in tubular cells probably via glomerulotubule crosstalk.

Funding: NIDDK Support, Veterans Affairs Support

PO1722

Podocyte-Specific Extracellular Vesicles Yield Novel Insight into Intercellular Signaling in the Glomerulus


Background: Extracellular vesicles (EVs) have been identified to play an essential role in basic pathological processes such as priming of the metastatic niche, autoimmunity and propagation of insulin resistance. Nevertheless, knowledge about their role in kidney health and disease remains scarce. A new group of EVs, shed upon apoptosis with the ability to induce a proliferative effect in neighboring cells, was recently identified in health and disease. Ongoing analyses aim to characterize their proteomic content and effect other renal epithelial cells. As these vesicles can be separated without advanced equipment such as ultracentrifuges, we believe they could also be a valuable source for biomarker research in various nephropathies.

Methods: Using differential centrifugation and filtration we established a protocol to separate medium-sized EVs from cell culture supernatants, kidney tissue and urine samples. We quantified the number of various podocyte-derived extracellular vesicles or podocyte-specific EVs exerted different effects on the proliferative and migratory behavior of primary parietal epithelial cells.

Results: Podocyte-specific medium-sized EVs were detected in baseline podocyte culture supernatant, untreated murine kidney tissue as well as the urine of healthy human volunteers. Vessel quantification revealed a drastic increase of vesicle release upon podocyte damage both in vitro and in vivo. Interestingly, podocyte-specific EVs exerted different effects on the proliferative and migratory behavior of primary parietal epithelial cells.

Conclusions: Our study represents the first investigation of podocyte-specific medium-sized vesicles, their release dynamics and functional implications in health and disease. Ongoing analyses aim to characterize their proteomic content and effect other renal epithelial cells. As these vesicles can be separated without advanced equipment such as ultracentrifuges, we believe they could also be a valuable source for biomarker research in various nephropathies.

PO1723

Effects of Varying Mild Tubular Injury on Subsequent Glomerular Injury

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Background: Tubular injury predisposes to CKD, including glomerular injury. We analyzed effects of mild tubular injury on subsequent glomerular injury.

Methods: Double transgenic, Nep25/DTR + male and female mice (with human CD25 receptor on podocytes and Diphtheria toxin (DT) receptor on proximal tubules) received DT (25, 50, or 100ng/kg; 2x one week apart, n=5/group) to induce tubular injury, or vehicle (VEH). Uninephrectomy was done 4 wks later; 5 wks later glomerular injury was induced by LMB2 toxin (CD25 ligand) and mice were sacrificed 10 days later.

Results: In males, urinary KIM-1 was significantly higher vs VEH with all DT doses on d3 after DT injections, lowest in DT50 and similar to DT50 and DT100. KIM-1 levels overexpressed additionally in males numerically in DT50 and DT100 vs VEH by wk 6. Urinary NGAL was significantly increased at d3 only in DT100 vs VEH. NGAL levels normalized in all DT groups by week 6. In females, KIM-1 levels were increased by d3 with highest level with DT100. KIM-1 levels were only numerically higher vs VEH in a dose-dependent manner in males. Urinary NGAL was increased at sacrifice after additional podocyte injury showed numerically higher levels by 67% in DT100 vs VEH. In females, albuminuria gradually increased, with levels lower than in males in all groups. Ultrastructural analysis after podocyte injury showed similar significant foot process effacement, glomerular capillary fenestration loss and increased GBM thickness in all groups.

Conclusions: Sex differences in response to tubular injury and albuminuria were observed. Even very mild tubular injury, recovered by assessment of KIM-1 and NGAL-1 led to numerical increase in albuminuria after second hit glomerular injury in both sexes. The sex-dependent differences in KIM-1 and NGAL-1 further support differential susceptibility of nephron segments to injury in females vs males, which may play a role in glomerular sensitization to injury.

Funding: NIDDK Support

PO1724

Effect of Glomerular Disease on the Podocyte Cell Cycle

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Background: Progression of glomerulosclerosis is associated with loss of podocytes and subsequent glomerular tuft instability. A decreased number of podocytes may be able to preserve tuft stability through cell hypertrophy associated with cell cycle re-entry. At the same time, re-entry into the cell cycle can lead to podocyte detachment from the glomerular basement membrane, if podocytes cross the G1/S checkpoint and undergo apoptosis.

Methods: To study cell cycle dynamics during CKD development, we used a Fucci mouse model (fluorescence ubiquitination-based cell cycle indicator) affected by X-linked Alport Syndrome (AS). This model has progressive CKD and expresses cell cycle fluorescent reporters exclusively in podocytes. We quantified podocytes cell cycle distribution in WT and AS mice at different ages and collected podocytes in G0 and G1 for proteomics studies.

Results: We showed that with the development of CKD, an increasing fraction of podocytes in vivo are in G1 or later cell cycle stages. G1 and G2 podocytes are hypertrophic. Heterozygous female mice, with milder manifestations of CKD, show G1 fraction numbers intermediate between WT and male AS mice. Proteomic analysis showed differences in cytoskeleton re-organization and metabolic processes between podocytes in G0 and G1 in different WT and WT/AS groups. WT and indicate alteration of specific proteins also identified in human AS podocytes.

Conclusions: Our data showed that, during progressive CKD, the podocyte cell cycle distribution changes dramatically, suggesting that cell cycle manipulation may have a role in the prevention and treatment of progressive glomerular diseases characterized by podocyteopathy.

Funding: Private Foundation Support

PO1725

Glucocorticoid- and Pigioglitazone-Induced Proteinuria Reduction Correlates with Glomerular Extracellular Matrix Remodeling in Experimental Nephritic Syndrome

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Background: Nephritic Syndrome (NS) is a common glomerular disease in children. While glucocorticoids (GC) are the mainstay of childhood NS treatment, pioglitazone (Pio; an FDA-approved PPARg agonist to treat type 2 diabetes) has been reported to reduce proteinuria in experimental NS and to directly protect podocytes from injury. Since both GC and Pio activate nuclear receptors (NR3C1 and PPARg, respectively) we hypothesized that their proteinuria-reducing effects result from overlapping glomerular gene transcriptional patterns.

Methods: We performed transcriptome analyses on glomeruli isolated from GC (immunosuppressive)- and Pio (non-immunosuppressive)-treated rats 11 days after induction of NS with PAN (n=4/group).

Results: Unsupervised clustering revealed partial reversibility of PAN-associated mRNAs; treatments with either GC or Pio IPA analyses + web-based bioinformatic platforms identified 29 genes-of-interest common to GC- and Pio-induced proteinuria reduction, which included ECM remodeling, lipid metabolism, DNA-binding and cytoskeletal organization. Based on expression differences using real-time PCR, gene expression downstream of Pio upregulated genes included those involved in extracellular matrix remodeling.

Conclusions: The expression of ECM remodeling genes is associated with Pio treatment in PAN-induced NS, suggesting that Pio may act through ECM remodeling to reduce proteinuria.

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Underline represents presenting author.
PO1726
Alteration of Intestinal Microbiota in Patients with ESRD Undergoing Hemodialysis
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Background: The alteration in the intestinal microbiota is reported to be associated with various diseases, indicating that the development and progression of end-stage kidney disease also might be associated with dysbiosis.

Methods: The stool samples were collected from patients with hemodialysis (n = 41, HD group) and those with normal renal function (n = 40, NRF group). Both groups are comprised of patients with (HD_DM, n = 20; NRF_DM, n = 19) and without diabetes (HD_non-DM, n = 21; NRF_non-DM, n = 21). We conducted 16S rRNA gene amplicon sequencing using stool samples to analyze the intestinal microbiota.

Results: The reduced abundance of the genera Megamonas and Fusosphaeribacter, and the enriched abundance of the genera Family_XIII_AD3011_group (Aeromonaraceae family), UBA_1819 (Ruminococcaceae family), and Pseudomonas in the stool samples of HD patients were observed significantly compared with those of NRF patients. Compared with patients with NRF DM, the relative abundance of the genera Megamonas was decreased and that of Family_XIII_AD3011_group was increased significantly in patients with HD DM, although those relative abundance did not alter between NRF_non-DM and HD_non-DM. The relative abundance of the genus Sutterella in HD_non-DM was significantly decreased than that in NRF_non-DM, although that relative abundance did not differ between NRF_DM and HD_DM. In the microbial beta diversity, there was no difference between NRF_DM and NRF_non-DM by weighted and unweighted Unifrac analysis, however, there was significant difference between HD_DM and HD_non-DM by unweighted Unifrac analysis (p = 0.007). These results suggest that the gut microbiota alters with renal function decline, and varies depending on the presence or absence of diabetes.

Conclusions: The intestinal microbiota might be varied substantially depending on renal function and the presence or absence of diabetes.

PO1727
Nutritional Intervention in Intensive Care Unit Patients Undergoing CRRT
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Background: Providing adequate calories and protein constitutes an important part of critical care, and inadequate nutrition for critically ill patients is associated with poor prognosis. Therefore, increased loss of amino acids, electrolytes, and water-soluble vitamins during continuous renal replacement therapy (CRRT) could be a therapeutic target. We evaluated whether enforcing protein, trace elements and vitamin supply could improve the prognosis of CRRT patients.

Methods: A nutritional intervention (100 mg/day of Thiamine, 25–30 kcal/kg of energy, 1.8 g/kg of protein, and 50–100 mcg/day of microelement with selenium) was provided in patients subject to CRRT from May 2020 to December 2020. The primary outcomes were 28-day mortality, CRRT day, ICU stay, and ventilator-free day, and the outcomes before and after the intervention were compared.

Results: Total 88 patients were included during the study period and compared with 88 patients in the previous year. The average age was 68.05 years old, 56 (63.5%) patients were male. At day 1 APACHE-II score was 35.45±11.9, SAPS3 88.1±16.8, SOFA 10.4±4.2. There were 9 (10.2%) patients with ECMO, 78 (88.6%) using ventilator. There were 19 (21.6%) pneumonia with ARDS patient, 18 (20.5%) cardiac disease, 9 (10.2%) UTE sepsis, 11 (12.5%) gastrointestinal bleeding and sepsis, 6 (6.8%) cerebral hemorrhage, and others. The main reason for CRRT was hemodynamic instability. Baseline characteristics including APACHE-II score, SAPS 3, and SOFA were not significantly different between the nutritional intervention and the non-intervention patients. Nutritional intervention did not induce any significant changes in 28-day mortality (36 versus 37, p = 0.56) and CRRT days (7.3 ± 6.9 versus 6.3 ± 5.2, p = 0.29). However, nutritional intervention showed minimal improvement in ICU stay (22.1 ± 23.9 versus 20.7 ± 22.1, p = 0.05) and ventilator-free days (17.8 ± 22.3 versus 12.4 ± 14.4, p = 0.05).

Conclusions: This study suggests that support for protein, trace elements, and vitamins may have a positive effect in CRRT patients. Therefore, the nutritional requirements of patients with CRRT should be carefully assessed, individualized, and considered as an important axis of CRRT treatment.

PO1728
Nutritional Phenotypes and Variation in Nutritional Parameter Trajectories Among Non-Dialysis CKD (CKD-ND) Patients Prescribed Oral Nutritional Supplementation
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Background: Among CKD-ND patients at risk of undernutrition/protein-energy wasting, the definition of patient subgroups most likely to benefit from ONS treatment is not known. Therefore, our aims were to identify phenotypes of non-dialysis CKD patients prescribed ONS, and to assess nutritional parameter slopes before and after ONS use, by phenotype.

Methods: This longitudinal cohort study included 2543 adult CKD-ND patients who entered multidisciplinary CKD clinics across British Columbia during 2010–2019, met weight and/or dietary intake criteria for ONS prescription based on dietitian assessment, received ≥21 ONS prescription. Hierarchical cluster analysis was used to identify phenotypes using baseline nutritional parameters. Using linear mixed models, slopes for body mass index (BMI), serum albumin, bicarbonate, phosphate, and neutrophil-to-lymphocyte ratio (NLR), an inflammation marker, were assessed in the 2-year periods before and after the first ONS prescription.

Results: Cluster analysis identified five nutritional phenotypes. Changes in parameter slopes (Aslope = post-ONS slope - pre-ONS slope) varied by cluster (Figure). Cluster 1 (characterized by the highest mean NLR and the lowest mean BMI among clusters) demonstrated statistically significant positive Aslopes for BMI, albumin and bicarbonate, and a negative Aslope for NLR. Cluster 2 (hypoalbuninemia) demonstrated positive Aslopes for BMI, albumin, and phosphate. Cluster 3 (low mean BMI) demonstrated a positive Aslope for BMI, accompanied by negative Aslopes for albumin and bicarbonate, and a positive Aslope for NLR. Cluster 4 (acidosis) demonstrated positive Aslopes for BMI and bicarbonate. In Cluster 5 (highest BMI), a negative Aslope for albumin and a positive Aslope for NLR were observed (no improvement with ONS).

Conclusions: The variation in response to ONS by cluster subgroup lends support to an individualized approach to nutritional management of patients at risk of undernutrition/protein-energy wasting.

Funding: Government Support - Non-U.S.
PO1730
The Beneficial Effects of Intradialytic Parenteral Nutrition in Malnourished Hemodialysis Patients: A Randomized Controlled Trial
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Background: Intradialytic parenteral nutrition (IPDN) is an intermittently supplemental nutrition support administered during hemodialysis (HD). IPDN has been suggested as a trial option after a failure response to oral nutritional supplement (ONS). However, the extent to which IPDN contributes to improve protein-energy status remains unclear.

Methods: Maintenance HD patients having spontaneous energy and protein intake of ≥ 29 kcal/kg/day and ≥ 0.8 g/kg/day, respectively, and intolerance to ONS were randomly assigned 1:1 to receive IPDN or intensive dietary counselling. In group 3, 1-3 anti-inflammatory omega 3-rich parenteral nutrition was infused during HD for 3 months followed by a treatment-free period of 3 months. The control group received an individualized dietary counselling once a week for 3 months to target the required nutrient intake. The outcomes were changes in serum albumin, muscle parameters and nutritional biomarkers. Serious adverse events were also monitored.

Results: A total of 38 patients were completed the study (age 67±11). Baseline characteristics were not different between groups. After 3 months, serum albumin was significantly higher in the IPDN (18) compared with control group (from 3.5±0.3 to 3.8±0.2 g/dL, p<0.01) and muscle mass was also significantly increased in IPDN (0.5±0.03% vs 0.01%, p<0.05). Among non-diabetic patients, IPDN significantly reduced serum IL-6 as an inflammatory marker (p<0.03) but unaltered serum acylated ghrelin as an orexigenic hormone (p=0.31). Muscle mass, strength, and serum prealbumin were not different between both groups. Participants in IPDN group reverted to baseline albumin levels after 3-month post-intervention follow-up. Neither volume overload nor uncontrolled hyperglycemia was found throughout the study.

Conclusions: A short-term IPDN supplementation significantly increased serum albumin level, a survival surrogate among HD patients. The impact of IPDN therapy on clinical outcomes may require larger scale with longer period of study.

PO1731
An Itch to Scratch: The Problem with Pruritus

Background: Dialysis patients often suffer from some level of associated pruritus and nephrologists generally recognize the condition’s impact on patient lives, rating pruritus as a high unmet need for new therapeutic options. However, official diagnosis of CKD-associated pruritus and physician-reported estimates may be highly underestimated.

Methods: Using a HIPAA-compliant, online chart review tool, 177 nephrologists submitted de-identified clinical and non-clinical demographic information for 1,008 dialysis patients in Fall 2020. These data were then merged with physician demographic profiles and attitudinal responses; the full data set was analyzed in SPSS.

Results: When thinking generally, nephrologists estimate that nearly one-half of end-stage renal disease (ESRD) patients on dialysis have some level of pruritus, making it extremely prevalent in this population. However, chart reviews reveal that only 3.2% of dialysis patients are diagnosed with uraemic pruritus (3.4% of HD patients and 1.4% of PD patients). On their last visit with their dialysis patients, nephrologists noted that only 4% of patients were treated (or they were told about pruritus, rash, itch, or pruritus) (3.7% of HD patients and 5.6% of PD patients). Interestingly, only approximately one-third of those patients were diagnosed with uraemic pruritus, indicating there are more patients presenting with a rash or itch who are not actually being diagnosed. Despite the impact on patient lives, nephrologists report that only 25% of HD patients diagnosed with uraemic pruritus are pharmacologically treated; this drops to 17% of PD patients with uraemic pruritus. Treatments vary wildly and have varying levels of reported success among physicians. Nephrologists do recognize the impact pruritus can have on a patient’s quality of life, making it a high rate of underdiagnosis especially troubling. On a 1-10 scale rating unmet need for a new therapeutic agent, 62% of nephrologists rated a high unmet need (8-10) for pruritis in dialysis patients.

Conclusions: While many recognize that itching impacts many dialysis patients, actual diagnoses and treatment are rare, driven by a lack of effective treatment options. Elevating awareness among nephrologists will help with patient identification and treatment, especially as new treatment options are available on the market to help patients.

PO1732
Long-Term Safety of Tenapanor for the Control of Serum Phosphorus in Patients with CKD on Dialysis: Serum Electrolytes and Albumin
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Background: Tenapanor, an investigational first-in-class phosphate absorption inhibitor (PAI), blocks the paracellular absorption of phosphate in the gastrointestinal tract by local inhibition of the sodium-hydrogen exchanger (NHE3). Tenapanor is being studied as a non-binder approach for the management of hyperphosphatemia in patients on dialysis and it is dosed as one pill (10, 20, or 30 mg) twice daily. Due to its novel mechanism of action, it is important to understand its safety profile, including any potential effects on serum electrolytes and albumin.

Methods: This report evaluates the effects of tenapanor on serum electrolyte and albumin concentrations using data from 3 pivotal trials in which tenapanor met its primary phosphorus-lowering endpoint. Trials included a 12-week monotherapy study (BLOCK), a 52-week monotherapy study (PIREDDOM), and a 4-week tenapanor + phosphate binder combination study (AMPLIFY). Serum electrolytes and albumin were measured per study protocol in central research laboratories.

Results: Tenapanor was generally well tolerated, with diarrhea being the only adverse event reported by ≥5% of patients. Diarrhea was typically mild to moderate in severity, was transient, and resolved with continued treatment. Data from all 3 trials showed that tenapanor treatment, either alone or in combination with phosphate binders, resulted in no clinically meaningful changes in measured serum electrolytes or albumin at any time point. Data from patients treated with tenapanor continuously for 52 weeks in the longest trial, PIREDDOM, are shown in the table.

Conclusions: In these clinical trials, tenapanor inhibited paracellular absorption of phosphate and decreased serum phosphorus with an acceptable safety profile, with no observed effect on serum electrolytes or albumin in patients on maintenance dialysis with hyperphosphataemia.

Funding: Commercial Support - Ardelxy, Inc.

PO1733
Patient-Reported Experience with Tenapanor in the OPTIMIZE Trial
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Background: Tenapanor (TEN), a first-in-class phosphate absorption inhibitor (PAI) that works via the paracellular pathway, provides a novel approach for hyperphosphatemia management. The primary goal of this study is to evaluate how to optimize the treatment of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis with the use of TEN and its novel mechanism of action.

Methods: Patients with serum phosphorus (P) ≥5.5 and ≤10.0 mg/dL during stable phosphate binder (PB) treatment were randomized 1:1 to 2 different treatment cohorts: Cohort 1 (straight switch; n=151) – discontinued current PB and began TEN 30 mg twice daily (BID); or Cohort 2 (50% PB reduction; n=152) – decreased current PB dose by 50% (or more if taking an odd number of PB tablets) and began TEN 30 mg BID. After week 2 investigators could increase PB doses to achieve sP ≤5.5 mg/dL with TEN as the core therapy. Additionally, patients on TEN with sP ≥5.5 mg/dL could add low dose PB, and patients on TEN and PBs with sP ≥5.0 mg/dL could reduce PB dose. Participants were monitored for safety and efficacy at weeks 0, 1, 2, 3, 4, 6, 8, and 10. At week 10 or the early termination visit, patients were asked about their experience with their sP management routine during OPTIMIZE compared to before the study. Here we report findings from a selection of questions from the patient experience questionnaires completed by a total of 179 patients in Cohort 1 and 179 in Cohort 2.

Results: When interviewed, 85.1% of patients in Cohort 1 and 83.5% of patients in Cohort 2 reported an improved perception of their sP management routine. Overall,
Decline in Glomerular Filtration Rate in CKD Stages 1 and 2

Health Maintenance, Nutrition, and Metabolism

Xiaoling

Apparently Paradoxical Relations of Serum Phosphate and Albumin Variability with Outcomes Are Explained by the Directional Change

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Background: Evidence indicates that variability of serum phosphate (P) and albumin (Alb) is associated with higher risk of mortality. We aimed to study the variability of P and Alb with all-cause mortality taking into account the interaction with the averaged levels.

Methods: All adult incident HD patients (pts) treated in Fresenius Medical Care NA clinics between 2010 & 2018 were included. Serum P and Alb levels were averaged from month(1) to 6 after HD initiation. Variability of P and Alb were described by standard deviation(SD) and directional changes(DR). All-cause mortality was recorded between mo 7 and 18. Cox proportional hazards models with spline terms were applied to explore the association between variability of P & Alb and all-cause mortality. Additionally, tensor product smoothing splines were computed to study the effect of interactions between averaged values of parameters and their variability with outcomes.

Results: We enrolled 353,142 pts. Averaged P was 4.98 mg/dL, median SD and DR were 0.92 and 1.10. Baseline Alb was 3.61 g/dL, median SD and DR were 0.21 and 0.40. Across different levels of P, higher SD of P were associated with higher risk of mortality, especially in those pts with lower averaged P. Contrasting, in pts with low Alb, higher SD was associated with reduced mortality. Regression analysis showed an unidirectional relation between DR and outcome was observed, whereas the relation between DR with outcomes was bidirectional for P (Fig1&2).

Conclusions: The relationship between P variability and mortality was apparent at all levels of P. In well-nourished pts, higher P variability are associated with increased risk of mortality, which is related to the adverse effects of both an increase and a decline of this parameter. In pts with low Alb, the apparently paradoxical association between higher levels Alb variability and better survival due to an improvement of nutritional and inflammatory status, related to a positive DR. Due to possible nonlinear relations between risk factors and outcomes in patients on HD, variability should ideally be explored by various metrics.

Restrict Dietary Phosphorus to Decrease Proteinuria and Prevent Decline in Glomerular Filtration Rate in CKD Stages 1 and 2

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Background: Though dietary phosphorus restriction is therapeutic for disordered phosphorus homeostasis, restriction of dietary phosphorus is not advised in CKD.

Aim: Does early control of dietary phosphorus ameliorates proteinuria, prevent decline in glomerular filtration rate and prevent rise in FGF-23.

Methods: One year longitudinal study on 79 CKD stages 1 and 2 patients. eGFR, serum creatinine, phosphorus, calcium, FGF-23, soluble o-Klotho iPTH FGF 23, blood pressure, were evaluated and compared with 35 controls. 3 days dietary intake was taken using standard methodology on first visit, 6 and 12 months. CKD patients were grouped based on dietary phosphorus intake: Group 1 (n=42): normal phosphorous intake (<1000mg/day) and Group 2 (n=37): high phosphorous intake (>1000mg/d).

Patients in Group 2 were educated on high and low phosphorus foods and counselled to adopt a plant-based diet, for low phosphorus absorption with directed diet plan. Data were analysed using SPSS.

Results: At baseline there was no significant difference in the GFR (group 1 85.00 vs 91.64 SD 13.22 vs 14.30) and serum creatinine between groups. In group 2; GFR, sKlotho, serum phosphorus and FGF23 correlated significantly with dietary phosphorus intake. In group 2, FGF-23, serum phosphorus, dietary protein and phosphorus intake were significantly higher and sKlotho was significantly lower than group 1. There was significant difference in serum phosphorus (p 0.000), iPTH (p 0.004), FGF23 (p 0.000), Klotho (p 0.000), urinary protein (p 0.000), dietary protein (Group 1 37.57±3.40; Group 248.79±8.66 p 0.000) and phosphorus (Group 1868.96±69.99 mg/d and Group 2 1312.26±137.57 mg/d p 0.000) intake and dietary phosphorus to protein ratio (p 0.000) between groups 1 and 2. On dietary intervention in group 2 FGF increased p 0.012 from 80.93±15.34 to 84.11±15.38, and to 87.43±18.27 ml/min at 6 and 12 months respectively, Urinary protein declined to 220.1±3.39 mg/L. FGF 23 declined from 60.67±6.26 to 58.00±7.07 to 53.29±9.48 pg/mL at 12 months. Dietary phosphorus: protein ratio reduced significantly from 27.16±4.33 to 24.75±4.34 p 0.000 at 12 months (p<0.000). Urinary phosphorus excretion increased from 574.37±214.22 to 624.64±137.67 at 12 months.

Conclusions: Restricting dietary phosphorus in stages 1 and 2 can prevent progression of CKD and for control proteinuria.

Understanding Obesity Management in CKD Patients


Background: Obesity is a global epidemic that is directly and indirectly linked to progression of chronic kidney disease (CKD). Nephrologists’ attitude towards obesity management is not understood.

Methods: We surveyed 14 nephrologists practicing in an academic centre in London, Ontario, Canada to investigate their perception and management of obesity. Then we performed a retrospective chart review of patients in a CKD clinic with obesity (BMI >30kg/m2). Ten follow-up visits were randomly selected for each nephrologist between Jan-Dec 2019. Each chart was assessed for documentation of obesity and a management plan such as lifestyle counselling, pharmacologic intervention, or specialist referral.

Results: There were 13 responses (93%). Responses from a 5-point Likert scale, agree and strongly agree, have been combined. All nephrologists agreed that obesity negatively impacts CKD patients. 92% reported that discussing obesity evokes a negative response and 39% thought patients want to discuss obesity. Interestingly, 0% of nephrologists thought patients know that obesity has effective treatments. 85% of nephrologists talked to their patients about obesity, but 0% felt that they had time to treat it. With regards to management, 54% of nephrologists were comfortable with non-pharmacologic treatment, but only one was comfortable with pharmacologic treatments. 85% of respondents felt that patients should be referred to a specialist. A total of 140 charts were reviewed with a mean age 66 years, weight 105 kg, and BMI 37 kg/m2. Only one chart had obesity as a clinical issue and documented a weight loss discussion using non-pharmacologic strategies.

Conclusions: Our results suggest that obesity is rarely managed despite nephrologists’ desire to treat it. This care gap can be addressed using robust Quality Improvement principles. Our centre will improve obesity management by developing a clinical handbook for nephrologists on how to efficiently address obesity with patients as well as a partnership and streamlined referral process to an obesity specialist.

Funding: Clinical Revenue Support

Changes over Time in DASH Diet Accordance by Racial/Ethnic Groups Among Us Adults

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Background: Recommendations for healthy dietary patterns may vary for individuals with and without CKD. Racial/ethnic disparities in dietary quality exist, yet there is limited understanding of how dietary patterns have changed over years in different racial/ethnic groups. We examined trends in accordance to a Dietary Approaches to Stop Hypertension (DASH) diet by different racial/ethnic groups in adults with and without CKD.
POI1738

Experiences of Participants of a Dietary Intervention Trial for African Americans with Hypertension and CKD


**Background:** African Americans are disproportionately affected by hypertension (HTN) and CKD and evidence suggests dietary modifications towards a more Dietary Approaches to Stop Hypertension (DASH) diet could improve outcomes for this population. We aimed to explicate barriers and facilitators of healthy eating, and the perceived benefits of the intervention among completed participants of a dietary intervention trial for African Americans with HTN and CKD. Participants were randomized to one of two groups: 1) Self-Shopping DASH (S-DASH) diet group with $30/week grocery allowance for 4 mo. but no specific guidance on purchases, followed by no food allowance for 8 mo.; or 2) Coaching DASH (C-DASH) diet advice group with a $30/week food allowance and assistance in purchasing foods for 4 mo., followed by intermittent coaching without food allowance for 8 mo.

**Methods:** We performed a content analysis of transcripts from semi-structured interviews with participants who completed the trial (13 C-DASH; 12 S-DASH were randomly selected). Thematic analyses followed 5 stages: 1) reading and rereading all transcripts and utilizing audio recordings as needed for clarity; 2) three coders reading two of the same transcripts, coding them, and comparing codes which were then used to create the initial coding framework; 3) defining codes, coding additional transcripts, discussing/ revising the coding framework; 4) formulating initial themes and 5) diagramming relationships among initial themes to merge overlapping themes.

**Results:** Participants were a mean age of 62 ± 9.3 years, 36% were male. Key themes included healthy diet facilitators (food tracking, motivation, social support, and perception of healthy foods); barriers (transportation, past eating habits, stress and COVID mitigation); and impacts of the intervention on knowledge and behavior.

**Conclusions:** Participants of a dietary intervention trial for African Americans with HTN and CKD identified several facilitators and barriers to healthy eating that could inform future efforts to address disease burden in this population.

**Funding:** Other NIH Support - NHLBI; NIMHD

POI1740

Barriers and Facilitators to DASH Diet Adherence Among Black Adults with CKD: A Qualitative Study

Crystal C. Tyson,1 Laura P. Svetkey,1 Isa Granados,1 Danielle L. Kennedy,1 Travia K. Dunbar,1 Pao-Hwa Lin,2 Gary Bennett,3 Cynthia H. Redd,1 L. Ebony Boulware,1 Laura J. Fish,3 Duke University School of Medicine, Durham, NC; 2Duke University, Durham, NC; 3Duke Cancer Institute, Durham, NC.

**Background:** Black individuals are disproportionately burdened by hypertension and chronic kidney disease (CKD). The Dietary Approaches to Stop Hypertension diet (DASH) improves hypertension in Black individuals and is associated with improved CKD outcomes. Yet, adherence to DASH among Black individuals is low. We conducted a qualitative study to assess barriers and facilitators to DASH adherence in Black adults with CKD.

**Methods:** We conducted focus groups and individual interviews with Black adults with CKD stages 3 or 4 (n=22). Questions included perceptions of DASH and DASH, the cultural-centeredness of DASH, and barriers and facilitators to adopting DASH. Qualitative content analysis was used to analyze interview transcripts.

**Results:** Among 22 participants (2 focus groups, 8 individual interviews), 13 (59%) had CKD stage 3, 13 (59%) were female, the median age was 61 years, and 19 (90%) had hypertension. Some participants reported having previously heard of DASH, which they perceived as a healthy diet. Participants perceived DASH as culturally-compatible and the perceived benefits of the intervention among completed participants of a dietary intervention trial for African Americans with HTN and CKD. Participants were randomized to one of two groups: 1) Self-Shopping DASH (S-DASH) diet group with $30/week grocery allowance for 4 mo. but no specific guidance on purchases, followed by no food allowance for 8 mo.; or 2) Coaching DASH (C-DASH) diet advice group with a $30/week food allowance and assistance in purchasing foods for 4 mo., followed by intermittent coaching without food allowance for 8 mo.

**Methods:** We performed a content analysis of transcripts from semi-structured interviews with participants who completed the trial (13 C-DASH; 12 S-DASH were randomly selected). Thematic analyses followed 5 stages: 1) reading and rereading all transcripts and utilizing audio recordings as needed for clarity; 2) three coders reading two of the same transcripts, coding them, and comparing codes which were then used to create the initial coding framework; 3) defining codes, coding additional transcripts, discussing/ revising the coding framework; 4) formulating initial themes and 5) diagramming relationships among initial themes to merge overlapping themes.

**Results:** Participants were a mean age of 62 ± 9.3 years, 36% were male. Key themes included healthy diet facilitators (food tracking, motivation, social support, and perception of healthy foods); barriers (transportation, past eating habits, stress and COVID mitigation); and impacts of the intervention on knowledge and behavior.

**Conclusions:** Participants of a dietary intervention trial for African Americans with HTN and CKD identified several facilitators and barriers to healthy eating that could inform future efforts to address disease burden in this population.

**Funding:** Other NIH Support - NHLBI; NIMHD
purchase healthy food after paying monthly bills. Facilitators included having local access to healthy food, living alone or with supportive household members, and having will power and internal/external motivation for change.

Conclusions: Black adults with CKD were interested in adopting DASH and viewed it as a healthy, culturally-compatible diet. Recognizing that diet in Black adults is not uniform, interventions should emphasize person-centered, rather than culture-centered, approaches that minimize barriers and enhance facilitators to adherence.

Funding: Other NIH Support - NHLBI

PO1741
Priorities for Person-Centered Obesity Management in ESKD

Background: Although obesity is a pervasive kidney transplant barrier, little is known about the social, dietary, and process-of-care challenges to addressing obesity among individuals with ESKD.

Methods: Using purposive sampling we recruited adults with ESKD and obesity (N=40) and ESKD health care professionals (HCPs, N=20) in the United States for semi-structured interviews to elicit perspectives about obesity and barriers and strategies for healthy weight loss. Recorded phone interviews lasting 1.5 hours were transcribed verbatim and analyzed using inductive and deductive thematic analysis.

Results: Median patient age was 55 (interquartile range [IQR] 47.63) years, median dialysis exposure was 5 (IQR 3.10) years, 51% were female, 27% were Black, and median BMI was 37.8 (IQR 33.5, 40.8) kg/m2. HCPs were renal dietitians, nephrologists, and transplant surgeons. Five themes emerged from patient interviews: 1) obesity-related counseling typically limited to immediate goal (transplant BMI requirements); 2) obesity as a life-long disease or linked to trauma; 3) food choices driven by fatigue and poor sleep quality; 4) existing nutrition programs not transferable to ESKD; 5) absence of culturally-effective nutrition counseling. HCP interviews revealed uncertainty about provider roles and responsibilities for addressing obesity and underscored that poverty and low health literacy are barriers to healthy weight loss.

Conclusions: Obesity-related care for people with ESKD is often limited to addressing BMI limits for transplant. Weight loss interventions for people with ESKD and obesity should be tailored with knowledge of social and financial context and a shift in focus from short-term goals to long-term health.

Funding: NIDDK Support

PO1742
Association of Nutritional Data and Glycemic Variability in CKD Patients

Background: Insulin resistance is highly prevalent in chronic kidney disease (CKD) and strongly associated with adverse clinical outcomes. Glycemic variability measured by continuous glucose monitoring (CGM) is a clinical measure of insulin resistance. The association of dietary recalls and healthy eating measures with CGM readings in CKD is unknown.

Methods: We recruited diabetic (n=7) and non-diabetic (n=8) participants with eGFR<60ml/min/1.73m2 and BMI 32.4±6.4kg/m2. Greater dietary added sugar, total carbohydrate, and carbohydrate to fiber ratio was associated with higher average daily blood sugar (P=0.001, P=0.001, and P=0.006, respectively). One-point greater HbA1c score (healthier eating) was inversely associated with average daily blood sugar for fatty acid (-1.09 mg/dL; 95% CI -2.11,-0.07), added sugar (-1.76 mg/dL; CI -3.11,-0.4), vegetable (-2.85 mg/dL; CI -5.5,-0.2), and fruit (-2.63 mg/dL; CI -5.03,-0.22). HEI total score did not show significant association with the CGM readings.

Conclusions: Greater added sugar, saturated fats, and dietary carbohydrate to fiber ratio are strongly associated with greater average daily blood sugar. Sugar, carbohydrates, and saturated fats contribute to glycemic variability. Healthy eating centered on low sugar, low fat, and high vegetable and fruit intake may improve glycemic control in both diabetic and non-diabetic CKD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

PO1743
Late Stage 3 CKD Is an Independent Risk Factor for Sarcopenia, but Not Proteinuria
Yong Seon Choi, Jung Nam An, Jwa-kyung Kim, Sung gyun Kim, Young rim Song. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.

Background: Most epidemiologic studies assessing the relationship between chronic kidney disease (CKD) and sarcopenia have been performed in dialysis patients. This study aimed to evaluate the relationship between estimated glomerular filtration rate (eGFR), proteinuria, and sarcopenia in patients with non-dialysis-dependent CKD.

Methods: A total of 892 outpatients who did not show any rapid changes in renal function were enrolled in this observational cohort study. We measured the muscle mass using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was found in 28.1% of the patients and its prevalence decreased as body mass index (BMI) increased; however, in patients with BMI ≥ 23 kg/m2, the prevalence did not increase with BMI. As eGFR decreased, the lean tissue index and HGS significantly decreased. However, the eGFR did not affect the fat tissue index. The risk of sarcopenia increased approximately 1.6 times in patients with eGFR < 45 mL/min/1.73 m2. However, proteinuria was not associated with sarcopenia. With a decrease in eGFR, the lean muscle mass and muscle strength decreased, and the prevalence of sarcopenia increased.

Conclusions: In patients with late stage 3 CKD, further assessment of body composition and screening for sarcopenia may be needed.

PO1744
Association of Serum Selenium Levels with the Response to Erythropoiesis-Stimulating Agents in Maintenance Hemodialysis Patients

Background: Reduced response to erythropoiesis-stimulating agent (ESA) has been shown to be associated with poor outcomes in maintenance hemodialysis (MHD) patients. Selenium is a trace element that modulates diverse physiological processes, such as immune responses and cardiovascular function. Previous studies also indicate that selenium and selenoproteins are involved in erythropoiesis. However, its role in the control of anemia in chronic kidney disease patients remains unclear. In this study, we determined serum selenium levels in MHD patients and analyzed their association with hemoglobin levels and the doses of ESA.

Results: Participants had a mean age 59±11years, eGFR 35.5±4.6ml/min/1.73m2 and BMI 32.4±6.4kg/m2. Greater dietary added sugar, total carbohydrate, and carbohydrate to fiber ratio was associated with higher average daily blood sugar (P=0.001, P=0.001, and P=0.006, respectively). Each 1-point greater HEI score (healthier eating) was inversely associated with average daily blood sugar for fatty acid (-1.09 mg/dL; 95% CI -2.11,-0.07), added sugar (-1.76 mg/dL; CI -3.11,-0.4), vegetable (-2.85 mg/dL; CI -5.5,-0.2), and fruit (-2.63 mg/dL; CI -5.03,-0.22). HEI total score did not show significant association with the CGM readings.

Conclusions: Greater added sugar, saturated fats, and dietary carbohydrate to fiber ratio are strongly associated with greater average daily blood sugar. Sugar, carbohydrates, and saturated fats contribute to glycemic variability. Healthy eating centered on low sugar, low fat, and high vegetable and fruit intake may improve glycemic control in both diabetic and non-diabetic CKD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

Poster

HEI-2015 Scores Associated with CGM in Non-Diabetic and Diabetic CKD Patients

<table>
<thead>
<tr>
<th>HEI-2015 Score</th>
<th>Average daily blood sugar (mg/dL)</th>
<th>Percent time above target (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEI Fat: Acid</td>
<td>-1.09 (-2.11, 0.07)</td>
<td>-0.34 (-1.85, 0.65)</td>
</tr>
<tr>
<td>HEI Added Sugar</td>
<td>-1.76 (-3.11, 0.4)</td>
<td>-1.15 (-2.24, 0.07)</td>
</tr>
<tr>
<td>HEI Total Vegetable</td>
<td>-2.95 (-5.3, -0.2)</td>
<td>-1.18 (-3.3, 0.08)</td>
</tr>
<tr>
<td>HEI Total Fruit</td>
<td>-2.63 (-5.03, 0.2)</td>
<td>-1.39 (-3.2, 0.59)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: The study included 174 patients who received MHD from four dialysis facilities. We obtained data on demographics, laboratory, comorbidities, hemodialysis prescription and medication by medical record abstraction. Concentration of selenium was measured in serum using ICP-MS.

Results: The mean age was 67.2 years, 77% were male, and 44% of patients received dialysis at least for five years. The average serum selenium concentrations in our cohort were 10.7 ± 2.9 µg/dL, and 88 patients (51%) had a selenium levels of less than 10.5 µg/dL (a lower limit of normal serum selenium levels for adult Japanese population). Patient characteristics, including age, sex, BMI, dialysis vintage, and comorbidities were not significantly different between the low selenium (Low) group and normal selenium (Normal) group. However, the percentage of patients receiving ESA tended to be higher in Low group than in Normal group, whereas hemoglobin levels as well as percentage of patients receiving iron therapy were similar between the groups. In a subgroup analysis involving 146 patients who received ESA, we found a significant negative correlation between serum selenium levels and ESA-resistance index (ERI) (r = -0.25, p = 0.002).

Conclusions: Our study indicates that low levels of serum selenium are associated with poor response to ESA. The relationship between selenium and response to ESA in MHD patients merits further evaluation in larger populations.

PO1745
Serum Irisin and Prediction of Cardiovascular Events in Elderly Patients with CKD Stage 3-5
Teresa Del Mastro, Teresa Arcidiacono, Monica Avino, Arianna Bologna, Nadia Edvige Foligno, Federico Persico, Giuseppe Vezzoli. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Irisin is a circulating myokine released from skeletal muscles after physical exercise. Irisin production decreases during the course of chronic kidney disease (CKD) as a potential consequence of sarcopenia and physical inactivity.

Methods: This observational study explored the relationship of serum irisin with cardiovascular outcome in 79 patients with stage 3-5 CKD.

Results: Serum irisin was significantly higher in healthy subjects (n=20) than CKD patients (7.2 vs 3.1±0.9 µg/ml; p=0.0001) and was higher in patients with CKD stage 3 (3.2±1 µg/ml) compared with patients at stage 4 and 5 taken together (n=36, 2.8±0.7 µg/ml; p=0.05). Patients in the lowest serum irisin tertile had lower serum 1,25(OH)2D levels (21 ±0.7 pg/ml, p=0.05). Patients in the highest tertile had lower Kaupilla score (10.6±6.9) than patients in the middle (11.8±5.5; p=0.007) and the lowest tertile (6.9±6.8; p=0.043). Twenty patients suffered from cardiovascular events during a 3-year follow-up. A Cox regression model using age, body weight, presence of diabetes mellitus, gender, Kaupilla calcification score, serum values of FGF23 (as logarithm), phosphate, sclerostin, albumin and cholesterol, eGFR and serum irisin tertiles as covariates showed that patients in the highest tertile of serum irisin had a lower cardiovascular risk than patients in the middle tertile (B=2.38, OR 10.8, 95%CI 1.65-58.13; p=0.013) or in the lowest tertile (B=1.61, OR 5, 95%CI 1.09-22.83; p=0.038).

Conclusions: These findings suggest that serum irisin may be a marker of cardiovascular outcome in CKD patients.
Conclusions: High dietary sodium intake is an independent risk factor for albuminuria and this association was highlighted in high Ucot/Ucrea group. The synergistic effects of cigarette smoking and high salt intake might increase the risk of albuminuria.

PO1748
Interplay Between Serum Thyrotropin, Free Thyroxine, and Thyroid Autoantibody Levels and Survival in a Prospective Hemodialysis Cohort
Amy S. You,1 Gregory Brent,2 John J. Sim,3 Yaltizzi Guerrero,4 Sara S. Kalantar,4,5 Rebecca Ahhdoot,6 Yoko Narasaki,6 Matthew D. Nguyen,6 Caspa P. Kovedsy,6 Danh V. Nguyen,6 Kamyar Kalantar-Zadeh,6 Connie Rhee,1 University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 2University of California Los Angeles Los Angeles Biomedical Research Institute, Anyang, Gyeonggi-do, Republic of Korea; 3S.invoke, Inc, Jackson, MS; 4University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 5Kaiser Permanente Southern California, Pasadena, CA; 6University of California Berkeley, Berkeley, CA; 7The University of Tennessee Health Science Center College of Medicine, Memphis, TN.

Background: CKD patients have a high prevalence of hyperthyroidism (elevated serum thyrotropin [TSH]) which has been associated with worse outcome. In patients with altered protein-hormone binding states (uremia, low/high circulating proteins) among whom routine “indirect” free thyroxine (FT4) assays are not as accurate, little is known about the impact of subclinical (high TSH-normal FT4) and overt (high TSH-low FT4) hyperthyroidism and thyroid autoimmune status on hemodialysis (HD) survival.

Methods: In a multicenter prospective cohort of 1117 HD patients from the “Hyperthyroidism, Cardiovascular Health, and Survival (HYCARDHS)” Study, we conducted protocolized TSH, “direct” FT4 by equilibrium dialysis/tandem mass spectrometry (robust FT4 assessment method in altered protein-hormone binding), and anti-thyroid peroxidase antibody (anti-TPO Ab) assays every 6 months from 2011-19. We examined associations of severity of thyroid dysfunction ascertained by TSH gradations (subclinical vs. overt hyperthyroid-range TSH levels) and pairings of TSH+FT4 (subclinical vs. overt hypothyroidism), as well as presence of elevated anti-TPO Abs with mortality using time-varying Cox models.

Results: TSH distributions were higher in those with elevated anti-TPO Abs. In analyses of TSH gradations, elevated TSH was associated with higher mortality (ref. 0.5-<3.0: HRs [95%CI] 1.30 [0.96-1.77] and 1.88 [1.31-2.68] for TSH 3.0-5.0 and >5.0. In analyses of paired TSH+FT4, overt hyperthyroidism was associated with higher mortality (aHR [95%CI] 5.11 [1.23-20.8], while subclinical hypothyroidism trended towards higher mortality (aHR [95%CI] 1.63 [0.98-2.72]). Elevated anti-TPO Abs were not associated with death.

Conclusions: In a prospective cohort of HD patients who underwent rigorous thyroid function assessment, both mild (subclinical) and severe (overt) hypothyroidism were associated with risk of death. Further studies are needed to determine if correction of thyroid status with thyroid hormone replacement therapy improves survival in this population.

Funding: NIDDK Support

PO1749
Effect of Water Intake and Water Balance on All-Cause and Cardiovascular Mortality Based on a Nationwide Population Study
Seonmi Hwang,1 Yaerim Kim,1 Jeonghwan Lee,2 Jae Yoon Park,3 Kyung Don Yoo,1 Yong Chul Kim,1 Dong Ki Kim,1 Yun So Kim,1 Chun Soo Lim,1 Jung Pyo Lee.1 1Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; 2Seoul National University Seoul Metropolitan Government Borumae Medical Center, Dongjak-gu, Seoul, Republic of Korea; 3Keimyung University, Seoul, South Korea.

Background: We aimed to investigate the relationship between daily water intake and mortality in patients with chronic kidney disease (CKD).

Methods: We conducted a prospective cohort study using data from the Korea National Health and Nutrition Examination Survey (KNHANES). A total of 117,484 participants aged over 19 years with no history of dialysis were included. The study population was categorized into quartiles based on water intake.

Results: The water balance consists of loss of water and intake of water. Healthy people maintain a good physiological water balance in their daily lives. The aim of this study was to investigate whether fluid intake is independently correlated with all-cause mortality among the general US adult population. In addition, we evaluated the relationship between daily water intake and mortality in patients with CKD.

Conclusions: In patients with CKD, higher water intake was associated with reduced mortality. Further research is needed to confirm these findings.

PO1750
Serum Cystatin C-to-Creatinine Ratio Is a Potential Biomarker for Sarcopenia in Patients with Non-Dialysis-Dependent CKD
Illeen Cho,1 Yong Seon Choi,2 Jung Nam An,3 Sung guny Kim,2 Young rim Song,2 Hallym University Sacred Heart Hospital, Anyang, Gyeyonggi-do, Republic of Korea.

Background: Sarcopenia is a prevalent complication in patients with chronic kidney disease (CKD) and linked with quality of life, morbidity and mortality. Sarcopenia is defined as clinical, functional and body compositional parameters, although several candidate biomarkers for this condition have been evaluated. This study aimed to evaluate serum cystatin C to creatinine (C(r)) ratio as a potential biomarker for sarcopenia in patients with non-dialysis-dependent CKD.

Methods: A total of 517 outpatients were enrolled in this observational cohort study. We measured the muscle mass ( lean tissue index, LTI) using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was observed in 25.5% patients. The serum cystatin C(r) ratio was significantly higher in patients with sarcopenia regardless of age, sex, eGFR, and BMI; and showed a positive correlation with age and pulse pressure, but LTI, HGS, hemoglobin, and serum albumin level showed a negative correlation with serum cystatin C(r) ratio. Especially in patients with eGFR > 45 mL/min/1.73 m2, serum cystatin C(r) ratio showed high negative predictive value in predicting sarcopenia (90.5%) and low LTI (90.4%). As the serum cystatin C(r) ratio increased by 1, the prevalence rate of sarcopenia and low LTI increased by about 5.8 times and about 9.9 times ever after adjusting for sex, age, BMI, undergoing dialysis, albumin, Hb, and eGFR. The association between serum cystatin C(r) ratio and sarcopenia was maximized in patients with eGFR less than 30, resulting in an increased prevalence risk of about 22.7 times, and in the case of low LTI, an independent association was found in patients with eGFR less than 45, and among them, a 43.9-fold increase in risk was identified. However, there was also no significant result for low HGS.

Conclusions: Serum cystatin C(r) ratio is inexpensive and easily, quickly, and repeatedly measured; therefore, quick screening and management of sarcopenia will be possible, which will be of great help in the treatment of CKD patients.

PO1751
Prevalence of Inflammation and Associated Healthcare Resource Utilization in Patients with CKD
Rachel Lai,1 Lynda Szczecz,2 Sarah Clayton,1 Lewis Harrison,1 Molly Lowe,1 James Jackson.2 FibroGen Inc, San Francisco, CA; 2Adelphi Group Ltd, Bollington, United Kingdom.

Background: Many patients with chronic kidney disease (CKD) suffer from inflammation, which often increases as CKD progresses. Inflammation is a risk factor for comorbidities and complications, as well as treatments for anemia. Increased inflammation has been associated with reduced red blood cell and erythropoietin production, as well as increased hepcidin levels, which can lead to functional iron deficiency. Because data on the impact of inflammation on healthcare utilization (HCRU) in patients with CKD are limited, we aimed to assess HCRU in these patients.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a point-in-time survey of physicians and their patients with CKD (stage 3-5D) collected in the United States in 2018. Physician and patient reported HCRU-related information, such as the number of healthcare visits, hospitalizations, and tests conducted to diagnose and monitor patients. Inflammation was defined as C-reactive protein ≥4.9 mg/L, ferritin ≥700 ng/mL, or albumin ≤3.6 g/L. Fisher’s exact and t-tests were conducted to assess differences in HCRU between patients with and without inflammation.

Results: There were 22,787 patients with eGFR < 60 mL/min/1.73 m2. The prevalence of inflammation was present in 136/491 (28%) non-dialysis-dependent, and 91/212 (43%) dialysis-dependent patients. HCRU, including the mean number of healthcare visits, tests conducted, and hospitalizations in the last 12 months, number of pills and injections taken per day, and days off work of requiring a carer were greater in patients with inflammation vs those without (all p<0.05; Table 1).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1752

Effects of Home BP-Based Behavioral Guidance on Urinary Albumin Excretion in School Workers with Microalbuminuria—Miyagi Karoshi Prevention Study

Masanori Yumakaka,1 Tomomi Hattori,1 Fumie Kubota-Nakayama,1 Sachiho Konno,1 Nobutaka Inoue,1 Tomohiro Nakamura,2 Atsushi Hozawa,3 Tohoku Rosai Byoin, Sendai, Japan; 2Kobe Rosai Byoin, Kobe, Japan; 3Tohoku Medical Megabank Organization, Sendai, Japan.

Background: Prevention of work-related cardiovascular events, or Karoshi is an important social issue in Japan. This study aimed to examine if home-BP based behavioral guidance is effective to reduce CV event risk in school staffs associated with microalbuminuria, a marker of endothelial damage.

Methods: Subjects were 3868 Miyagi prefectural school workers. Urinary albumin excretion adjusted for creatinine (UAE) and daily sodium intake based on Tanaka method were examined together with usual annual health check-up in 2019. Among them, 169 were diagnosed as having microalbuminuria (30-299.9mg/gCr). Ninety-one subjects agreed to receive the home-BP based health guidance. Guidance was given according to 5 days mean BP levels. UAE was examined at baseline in 2019, and one year after the guidance was given.

Results: Final analysis number was 48 and 43 for guided and non-guided groups. Subjects with menstruation were excluded from analysis. Reduction in UAE did not differ between groups with or without home-BP based behavioral guidance. Our data suggest that notification of microalbuminuria per se have considerable degree of favorable behavioral effects in school workers with microalbuminuria.

Funding: Government Support - Non-U.S.

PO1753

Weight Changes Following Diabetes Medication: A Population-Based Study

Bojin Lyu,1 Morgan Grams,2 Lesley A. Inker,3 Alex R. Chang,4 Jung-Jin Shim,3 1University of Wisconsin-Madison, Madison, WI; 2Johns Hopkins Medicine, Baltimore, MD; 3Tifs Medical Center, Boston, MA; 4Geisinger Medicine, Danville, PA; 5Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.

Background: The majority of patients with type 2 diabetes are obese, with greater percentages in those with concomitant CKD. Clinical trials suggest that the newer glucose-lowering medications, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like-peptide-1 receptor antagonists (DPP4i), provide an added benefit of weight loss in people with type 2 diabetes. We evaluated the magnitude of weight change associated with diabetes medication prescription in real-world practice in persons with and without CKD (eGFR <60 vs. ≥60 ml/kg/1.73 m²).

Methods: We identified patients with diabetes who initiated SGLT2i (n=925), GLP1RA (n=1571), and DPP4i (n=2206) between 2015 and 2018 in Geisinger Health System. Outcomes were percent weight change per year among all patients within 1 year after medication initiation and time to first achieving 5% weight loss among patients with obesity/obesity at medication initiation. Inverse probability of treatment weighting (IPTW) based on multinomial propensity scores was used to account for differences in baseline patient characteristics by medication class.

Results: The mean (SD) age of the 6919 patients was 58 (14) years and 3381 (49%) were female. Comparisons with SU, SGLT2i, GLP1RA, and DPP4i were associated with significant weight loss, with stronger associations for SGLT2i and GLP1RA (Table). Similarly, SGLT2i, GLP1RA, and DPP4i users were more likely to achieve 5% weight loss compared with SU (HR [95% CI]: 1.47 [1.28, 1.69] for SGLT2i; HR: 1.55 [1.32,1.82] for GLP1; HR: 1.31 [1.19,1.44] for DPP4i). The associations were consistent across CKD stages.

Conclusions: In patients with and without CKD, SGLT2i and GLP1RA were associated with significant weight loss compared with SU. These results may further motivate uptake of SGLT2i and GLP1RA, two classes of medications with proven renal benefits among patients with overweight or obesity.

Funding: NIDDK Support

Percent weight change (%/year) within 1 year associated with diabetes medications

PO1754

Effects of Caloric Restriction and Aerobic Exercise on Circulating Cell-Free Mitochondrial DNA in Patients with Moderate-to-Severe CKD

Javier Jaramillo Morales,1 Berfu Korucu,2 Mindy Pike,1 Sam A. Headley,2 BethAnn Micaronamara,3 Judit St. L. C. R. Tuggle,2 Jonathan Meade,2 Cassianne Robinson-Cohen,2 Talat Alp Ikizler,1 Jorge Gamboa.1 1Vanderbilt University Medical Center, Nashville, TN; 2University of Washington, Seattle, WA; 3University of California Davis, Davis, CA; 4Springfield College, Springfield, MA.

Background: Understanding mechanisms for increased oxidative stress and inflammation in patients with chronic kidney disease (CKD) is vital due to their role in the pathophysiology of this population. Circulating cell-free mitochondrial DNA (ccf-mtDNA) is released to the plasma and believed to promote inflammation by acting as a damaged-associated molecular pattern. Previous studies suggested that in patients with kidney disease, ccf-mtDNA increases and may induce inflammation. Past investigations in patients with CKD have found that aerobic exercise decreases inflammation. We hypothesized that in patients with moderate to severe CKD, aerobic exercise would reduce plasma levels of ccf-mtDNA.

Methods: We performed a post hoc analysis of a multi-center pilot randomized trial of aerobic exercise and caloric restriction (NCT01150851). We measured ccf-mtDNA in plasma at baseline and four months after four interventions (aerobic exercise (EX), caloric restriction (CR), EX + CR, usual activity and usual diet). A multivariable model adjusted for age, race, sex, systolic BP, BMI, diabetes, and eGFR was done.

Results: Of a cohort of 111 participants who were randomized, 99 had baseline ccf-mtDNA levels, and 92 completed the study. The median age was 57 years old, 44% were female, and 92% had diabetes. Plasma ccf-mtDNA median concentrations at baseline, two, and four months were 3.62, 3.08, 2.78 pM for the usual activity group and 2.01, 2.20, 2.67 pM for the aerobic exercise group. There was a 16.1% increase per month in ccf-mtDNA in the aerobic exercise group compared to the usual activity group (p < 0.024), especially with the combination of aerobic exercise and caloric restriction (29.5% increase per month). After four months of intervention, ccf-mtDNA increased in the aerobic exercise group by 81.6% (95% confidence intervals [CI] 8.2-208.4; p = 0.024) compared to the usual activity group, but it was only observed in the aerobic exercise and caloric restriction group (181.7% increase, 95% CI 41.1-462.2; p = 0.003).

Conclusions: Our data suggest that aerobic exercise increases plasma ccf-mtDNA levels in patients with CKD stages 3-4, more profoundly in ones with a combination of caloric restriction.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIEHS, NCATS

PO1755

Physical Activity in Patients Undergoing Dialysis: A Pilot Study

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Background: Patients on chronic dialysis have impaired physical function and poor quality of life. Slow gait speed and handgrip strength are indicators of increased all-cause mortality and cardiovascular events in dialysis patients. The relationship between physical activity and gait speed is inconsistent in prior studies. "Cadence", a gait characteristic measured as steps/minute by accelerometer is strongly associated with walking speed and physical activity. We hypothesized that cadence will be lower in dialysis patients compared to healthy adults and that cadence will be correlated with their gait speed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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Poster 543
Methods: Physical activity was measured in N=20 subjects incident to dialysis over 7 days using a validated wrist worn tri-axial accelerometer (ActiGraph). The 7 days included dialysis and non-dialysis days. Average daily cadence (steps/sec) was extrapolated from accelerometer data utilizing a published algorithm. Subject demographics were recorded by self-report or from medical records. Gait speed (meter/sec) was measured over 4 meters. Data on cadence from healthy subjects (N=32) were obtained from a prior study.

Results: Of twenty subjects (4 peritoneal dialysis, 16 hemodialysis), no one recorded any vigorous activity in the entire period, while most (59.4%) of their time was spent in sedentary behavior. Median average daily cadence across subjects was 1.38 [IQR = (1.31 – 1.48)] steps/second. Dialysis subjects had lower average daily cadence than healthy subjects (1.38 vs 1.66 steps/second, p = 0.001). When adjusted for age and sex, being “on dialysis” was associated with a 0.24 (95% CI -0.34, -0.14) steps/second lower cadence compared to healthy subjects. For patients on hemodialysis, average daily cadence was not significantly different between HD days and non-HD days, with no significant correlation between 4m speed and cadence (r=−0.28).

Conclusions: In this prospective study, we show that cadence is low in dialysis patients, that dialysis patients are sedentary and cadence does not correlate with gait speed. Thus gait speed alone may not be an accurate representation of intensity of daily physical activity. This pilot study supports the need for detailed studies of gait characteristics in dialysis patients, which will help in the development of personalized exercise and activity programs in patients undergoing dialysis.

PO1756

Physical Activity Scores in Hemodialysis Patients with Thyroid Dysfunction: A Substudy of the NIH THYROID-HD Trial

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Background: Low physical activity is common in hemodialysis (HD) patients and is associated with adverse outcomes in this population (poor health-related quality of life, cardiovascular [CV] disease, death). Prior studies show that hypothyroidism is highly prevalent in HD patients, and is associated with worse self-reported physical function.

Methods: In a substudy of the ongoing multi-center NIH THYROID-HD Trial, we examined baseline physical activity scores determined by the Human Activity Profile (HAP), a validated 94-item instrument assessing daily activities across a wide range of energy expenditures, in HD patients with TSH levels in the high-normal (TSH >3.5 mIU/L) and subclinical hypothyroid range (TSH >5-10 mIU/L). The HAP was used to derive the Maximum Activity Score (MAS) and Adjusted Activity Score (AAS), representing greatest and mean estimated energy expenditures, respectively (range 0-94, segmented to low [<52], moderate [54-73], and high [>74] scores).

Results: Among 57 HD patients who underwent baseline HAP assessment, the mean±SD MAS and AAS scores were 52±21 and 26±27, respectively; median (IQR) MAS and AAS scores were 52 (40, 68) and 22 (6, 49), respectively. In the overall cohort, 79% had low, 14% moderate, and 7% high AAS scores. MAS scores were lower in patients who were older (≥65 yrs), female, White, Hispanic, of longer (>1 yr) vintage, diabetic, or with underlying CV disease. A similar trend was observed for AAS scores.

Conclusions: In this substudy of the NIH THYROID-HD Trial, HAP scores in HD patients with high-normal and subclinical hypothyroid range TSH levels were lower than observed in prior historical dialysis cohorts that did not have underlying thyroid dysfunction. Further research is needed to determine the impact of thyroid hormone replacement on improving physical activity and function in this population.

Funding: NIDDK Support
**PO1758**

**Comparisons of In-Clinic and Free-Living Measures of Physical Function in Predicting Hospitalization in Patients with CKD**

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**Background:** Physical function is associated with risk of hospitalization; however, comparisons of in-clinic and free-living measures of physical function and their associations with risk of hospitalization has not been well established.

**Methods:** In this secondary analysis of the Sit Less, Interact, Move More (SLIMM) pilot study, we compared in clinic and free-living measures using accelerometry data. Participants with CKD were randomized to the SLIMM intervention or standard of care and asked to wear a thigh worn accelerometer 7 days before a visit to capture their physical activity. In clinic measures of physical function like 6-minute walk distance were performed during visits. Free-living measures were determined from accelerometry. Free-living 6-minute steps were defined as the number of steps taken during the most active 6-minute period. Free-living measures of physical function were compared to in clinic measures using Cox proportional hazards models adjusted for age, sex, smoking, alcohol use, BMI, diabetes, CKD, hypertension, heart failure, and peripheral vascular disease.

**Results:** 106 participants were randomized, the mean age was 69 ± 12 and 69 ± 14, baseline eGFR was 44 ± 12 and 45 ± 14, and 48% and 37% were female for the standard of care and SLIMM groups respectively. When adjusted for covariates, both in clinic and free-living 6-minute walk distance and steps respectively were associated with hospitalizations (table). In comparisons between in clinic and free-living measures, in clinic measures were not significantly associated with hospitalizations while free-living measures were (table).

**Conclusions:** Both in clinic and free-living measures of physical function were predictors of hospitalization in patients with CKD.

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

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**PO1759**

**Blood Pressure Trends in a Cohort of 9- and 10-Year-Old Children in Iceland: A 10-Year Follow-Up Study**

Asdis H. Sigurdardottir,1,2 Olafur S. Indridason,3 Sigurdur S. Stephenson,3 Thordis J. Hrafnkleidsson,1 Vidar O. Edvardsson.1,4 1Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland; 2Children’s Medical Center, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; 3Division of Nephrology, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; 4Division of Cardiology, Landspitali-The National University Hospital of Iceland, Reykjavik, Iceland.

**Background:** Although there is significant evidence for an association between childhood and adult office blood pressure (BP), data on the correlation of childhood BP and ambulatory BP (ABP) in young adults is missing. The aim of this study was to examine the association between childhood office BP and both ABP and office BP indices in a cohort of young adults born preterm and follow-up BP.

**Methods:** Subjects were recruited from a cohort of 970 young adults aged 20-21 years who participated in a population-based study of BP in 9-10-year-old Icelandic school children. All participants underwent a minimum of 4 resting BP measurements at the childhood BP screening. A total of 121 individuals have completed their participation in the follow-up study, which included office and ambulatory BP measurements. Pearson correlation and linear regression analysis were used to examine the relationship between childhood and follow-up BP.

**Results:** A significant positive correlation was observed between childhood mean systolic BP (SBP) and systolic and office BP at follow-up (r=0.386, p<0.001 and r=0.370, p=0.001, respectively). The correlation between childhood mean systolic office BP and follow-up mean systolic office BP was stronger for males (r=0.50, p<0.001 than for females (r=0.298, p=0.012), and the same applied for mean systolic ABP (r=0.491, p<0.001 and r=0.323, p=0.006, respectively). The correlation of mean childhood diastolic office BP and follow-up mean DBP indices at follow-up was insignificant for males (office DBP: r=0.05, p=0.78) and remained significant for females (office DBP: r=0.55, p=0.0026; ABP: r=0.449, p<0.001). In adjusted analysis, childhood mean office SBP significantly associated with mean office SBP at follow-up in both males (beta=0.69, p<0.001) and females (beta=0.26, p=0.001). Each mmHg increment in childhood office SBP predicted an increase of mean ambulatory SBP by 0.52 mmHg (p<0.001), unaffected by sex. Childhood DBP did not significantly predict office or ambulatory BP at follow-up in adjusted analysis.

**Conclusions:** These preliminary results indicate that childhood SBP significantly predicts both systolic office and ambulatory SBP in young adults and these associations are stronger in males.

**Funding:** Government Support - Non-U.S.

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Underline represents presenting author.

**PO1760**

**Preterm Birth and Its Association with Altered Renal Sodium Handling in Response to Mental Stress in Young Adults**

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**Background:** Early-life programming events such as preterm birth and very low birth weight (VLBW; <1500 g) contribute to later hypertension development, but the underlying mechanisms are unknown. Experimental data suggest that altered pressure natriuresis and renal sodium handling may be important contributing mechanisms. Adults with primary hypertension exhibit blunted pressure natriuresis in response to sympathetic arousal, but this has not been described in adults born preterm. We investigated renal sodium excretion relative to the change in blood pressure (BP) in response to stress in a cohort of young adults born preterm with VLBW. We hypothesized that young adults born preterm will have a blunted pressure natriuresis response to mental stress compared to those born term with normal birth weight.

**Methods:** In this long-term prospective cohort of 161 individuals, 129 (80%) born preterm with VLBW and 32 (20%) term-born controls, we measured spot urine sodium/creatinine before and after a 30-min mental stress test and non-invasive continuous BP every 2 min during the stress test. We defined our outcome, pressure natriuresis, as the change in sodium excretion relative to the change in mean arterial pressure (MAP) and defined our exposure variable as the stress test with a blunted response being < 0 mg/dl per mmHg. We used generalized linear models to estimate the association between prematurity and the outcome.

**Results:** The mean age of study participants was 19.8 (SD 0.9) of whom 56% were females. The absolute change in sodium excretion relative to change in MAP was 0.022 mg/dl per mmHg [90. -0.021, 0.121], while the change in term-born counterparts was 0.04 mg/dl per mmHg [0.005, 0.184]. On unadjusted analyses, the preterm/term difference in pressure natriuresis was 0.068 mg/dl per mmHg [-0.092 to 0.239] and the relative risk of a blunted pressure natriuresis was 1.3 (0.71 to 2.36).

**Conclusions:** We observed no statistically significant difference in pressure natriuresis response in adults born preterm with VLBW when compared to those born term. Ongoing analyses include investigating other measures of pressure natriuresis in adjusted multivariable models.

**Funding:** NIDDK Support

**PO1761**

**The Cardiovascular Risk Analysis According to Different Pediatric Hypertension Guidelines: Data from the Korea National Health and Nutrition Examination Survey, 2016-2018**

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**Background:** Worldwide pediatric hypertension (HTN) prevalence is increasing. Pediatric HTN predicts adulthood HTN, the modifiable leading factor of cardiovascular disease (CVD). Therefore, pediatric HTN is important for CVD risk prevention. There are two well-known pediatric HTN guidelines, the 2017 American Academy of Pediatrics (AAP) and the 2016 European Society for Hypertension (ESH). Also, Korea Center for Disease Control established the blood pressure (BP) classification in 2008 (K-CDC). There is discordance of HTN prevalence in each BP classification. However, no study evaluated the CVD risk according to each BP criteria in the Korean pediatric population. This study evaluated the difference in prevalence and pediatric CVD risk factors according to each BP criteria.

**Methods:** The data of 2060 children and adolescents aged 10-18 years from the Korea National Health and Nutrition Examination Survey 2016-2018 was reviewed. The BP was classified by AAP, ESH, K-CDC and modified AAP (K-AAP, applying the normal weight Korean children BP reference table in AAP definition). The high BP was defined when BP was above normotension. To analyze the difference in CVD risk, AAP and ESH, K-CDC and K-AAP and K-CDC were compared. In each comparison, those newly defined as high BP are compared to those with consistent normotensive - age, sex, height matched. Finally, the BP criteria reflecting more CVD risk was used to analyze data from Korea School Health Examination Survey 2018.

**Results:** The prevalence of high BP in Korean children and adolescents was generally high in AAP than ESH (19.5% vs 10.6%, p<0.001). However, there were some differences in prevalence according to age, sex and obesity. AAP reflected more CVD risk factors, including obesity and metabolic risk, than ESH. K-AAP well-screened non-obese children with metabolic risk than AAP and children with obesity and metabolic risks than K-CDC. The prevalence of high BP and HTN in Korean school students with K-AAP was 13.7% and 5.1%, respectively.

**Conclusions:** The K-AAP classifies Korean children and adolescent with more CVD risk factors as high BP. Therefore, for early CVD risk control, K-AAP could be used to define pediatric HTN in Korea. Further study is warranted for actual CVD association.
PO1762
Clinical Event Reductions in Hypertension Patients with and Without CKD Treated with Renal Denervation: A Model-Based Estimate Based on Data from the Global SYMPLICITY Registry

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Background: Estimates of clinical event reductions following renal denervation (RDN) were modelled for patients with and without chronic kidney disease (CKD) based on data from the Global SYMPLICITY Registry (GSR). 2) standard well-C (SBP 120-130 and DBP <80 mmHg), 2) standard well-C (SBP <120 and DBP <70), 3) standard well-C (SBP 120-130 and DBP 80-90), and 4) standard well-C (SBP 120-130 and DBP 90-100). The overall incidence rate (IR) for the well-C standard group. The study outcomes were investigated using multivariate Cox-regression analysis after adjusting for clinical variables.

Methods: 1. The study cohort consisted of male, non-smoking individuals, aged 27 ± 11 years. We analysed the renal hemodynamic using steady state input clearance method. Results: Among the 502 participants, the following parameters: RPF (p = 0.006), GFR (p = 0.017), RBF (p = 0.006), RVR (p = 0.02), and APWV (p = 0.005).

Conclusions: Uncontrolled hypertension increased risk for MACCE and all-cause mortality in patients with or without MetS, whereas intensive control of BP also increased risk. Therefore, properly targeting the blood pressure is important to reduce the risk of major clinical outcomes irrespective of the presence of MetS.

PO1764
Vascular Function Indices Are Strong Predictors of the Severity and Characteristics of Carotid Atherosclerosis

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Background: Vascular functional indices strongly predict adverse cardiac outcomes in CKD. However, few have examined the link between vascular function and the severity and characteristics of carotid atherosclerosis in CKD. Management of Cardiovascular disease in CKD(McK, NCT03563152) is a randomized controlled study aimed to evaluate the effects of hydroxychloroquine on inflammation, vascular dysfunction and carotid atherosclerosis in Veterans with high-CV risk CKD. Analyzing the baseline parameters of enrollees, we aim to evaluate the predictors of carotid atherosclerosis in CKD patients.

Methods: All randomized participants of Mcck study underwent detailed clinical and laboratory evaluations, including evaluation of carotid atherosclerosis (main atherosclerotic burden and carotid intima-media thickness), vascular function (central aortic pressure (CAP), augmentation index (AI), and aortic pulse wave velocity (APWV) by sphygmocore™ XCEL) and detailed evaluation of carotid atherosclerosis 15 mm above bifurcation (total plaque volume (TPV), lipid-rich necrosis, calcification, fibrous cap, and intraplaque hemorrhage by 3T MRI analyzed with Plaqueview™ software).

Results: Initial 17 randomized participants(age 73±4years, all males, 41% with pre-existing CKD and 88% on statins, with eGFR 40±6ml/min/m², microalbuminuria/creatinine ratio (MCR) 1912±7270mg/gm, hsCRP 10.6±20.6ng/mL, total cholesterol 168±40mg/dL, and LDL/ HDL ratio 2.1±0.7) with full analyzable MRI were included in the analysis. Significant vascular stiffness was evident at baseline with CAP 98.3±12.6 mmHg, Augmentation Index:15.5±7.6 and APWV:9.3±2.4 m/s. Atherosclerotic burden was high, carotid TPV:3.7±1.0cm³ and Normalized Wall Index:71.7±9.4, with necrotic core, calcification, fibrous cap, and intraplaque hemorrhage volumes of 357.6±289, 556.2±478, 153.8±122 and 49.6±78 mm³ respectively. Univariate analysis showed that detailed baseline clinical and laboratory parameters had no significant correlations with TPV or its individual components whereas, vascular functional indices had strong positive correlations with TPV and individual plaque components(p<0.01, especially the CAP), which had among the strongest correlations with lipid-rich necrotic core (p<0.000).

Conclusions: Non-invasively measured central aortic pressure and aortic pulse wave velocity are strong predictors of carotid atherosclerosis and unstable plaques.

Funding: Veterans Affairs Support}

PO1765
Relation Between Waist Circumference and Renal Hemodynamics in Healthy Individuals

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Background: Abdominal adiposity, measured by waist circumference (WC), is associated with increased mortality in individuals with chronic kidney disease. Little is known about the impact of abdominal obesity on the renal perfusion and function in humans. We analyzed whether abdominal adiposity changes renal hemodynamics in 80 healthy, young, male individuals without cardiovascular (CV) disease.

Methods: We analysed the renal hemodynamic using steady state input clearance method. Results: Among the 502 participants, the following parameters: RPF (p = 0.006), GFR (p = 0.017), RBF (p = 0.006), RVR (p = 0.006), and APWV (p = 0.005).

Conclusions: Non-invasively measured central aortic pressure and aortic pulse wave velocity are strong predictors of carotid atherosclerosis and unstable plaques.

Funding: Veterans Affairs Support
Patients with CKD and Multiple Chronic Conditions Are at Increased Risk of Cardiovascular Events


Background: Major adverse cardiovascular events (MACE) are the leading cause of mortality in chronic kidney disease (CKD). We studied the relationship between the number and type of multiple chronic conditions (MCCs) and the risk of MACE in patients with CKD.

Methods: We retrospectively examined the SAIL database: a cohort consisting of the population of Scotland, UK (2011-2018). Patients were categorised by the number of MCCs additional to CKD: the primary analysis included all MCCs (e.g. asthma, depression), and a secondary analysis excluded cardiometabolic conditions (hypertension, ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation, peripheral vascular disease, diabetes). The outcome was MACE: myocardial infarction, stroke, heart failure hospitalisation. The risk of MACE associated with number of MCCs was calculated using Cox proportional hazards models. Adjustments were made for age, sex, smoking, deprivation, eGFR and cholesterol.

Results: Of the 173,388 patients with CKD, median age was 78 years, 57% were female, 98% were of white ethnicity and median eGFR was 51.8 ± 17.3 mL/min/1.73m². There was a graded rise in the risk of MACE by MCC count (Table 1): 1 condition adjusted hazard ratio (aHR) 1.15 (1.02-1.29), 2 MCCs aHR 1.37 (1.22-1.53), 3 MCCs 1.68 (1.50-1.88), 4+ MCCs 2.61 (2.34-2.92). For non-cardiometabolic conditions, MACE risk was lessened, but the trend persisted: 1 condition aHR 1.16 (1.12-1.20), 2 MCCs aHR 1.30 (1.25-1.35), 3 MCCs 1.43 (1.38-1.49), 4+ MCCs aHR 1.65 (1.59-1.71).

Conclusions: Patients with CKD and MCCs are at high risk of MACE, even when cardiometabolic conditions are excluded. Cardiovascular risk stratification and preventative strategies in patients with CKD should take into account the number and type of other chronic conditions.

Funding: Other NHRI Support - Medical Research Council (UK)

Table 1: Data are presented as mean ± SD

POI1776

Framingham Risk Score and ACC/AHA Pooled Cohort Equation for Prediction of Atherosclerotic Cardiovascular Events in CKD

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Background: The Framingham Risk Score and the ACC/AHA Pooled Cohort Equation are used clinically to identify patients at high risk for atherosclerotic cardiovascular disease (ASCVD). The performance of these equations (alone or with clinically available cardiac biomarkers) is unclear in patients with chronic kidney disease (CKD), particularly at more advanced stages. We tested the discrimination of these risk scores and cardiac biomarkers to predict ASCVD in CKD.

Methods: We studied 1027 participants in the Chronic Renal Insufficiency Cohort without ASCVD who were not taking aspirin or statins. Framingham Risk Score, Pooled Cohort Equation, N-terminal pro-brain type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT) were measured at baseline. Outcomes were the composite of fatal and non-fatal myocardial infarction (MI) and cardiac death, with or without stroke, over 10 years. We estimated internally valid C-indices using a Wald cross validation for each risk score and cardiac risk marker overall, and across categories of eGFR.

Results: Among 1027 participants, the mean age was 52 years, and the mean eGFR was 48 mL/min/1.73 m². The C-index (95% CI) was 0.74 (0.69, 0.79) for the Framingham Risk Score, and 0.72 (0.67, 0.78) for the Pooled Cohort Equation. Both risk scores had better discrimination for predicting ASCVD at eGFR >60 mL/min/1.73 m² compared with lower eGFR. HsTnT had comparable discrimination to both risk scores overall. HsTnT alone had comparable discrimination across the spectrum of CKD severity (difference in C-index for lowest vs highest eGFR category for ASCVD 0.04-0.05, 95% CI -0.21, 0.14) (Table).

Conclusions: The Framingham Risk Score and Pooled Cohort Equation had moderate discrimination for prediction of ASCVD in CKD and performed better at eGFRs >60 versus <60 mL/min/1.73 m². HsTnT alone had discrimination comparable to each risk score overall, and comparable discrimination across the spectrum of CKD severity.

Further work is needed to develop novel risk scores including cardiac biomarkers specifically for use in CKD.

Funding: NIDDK Support

POI1768

Nondipping Heart Rate in Patients with CKD

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Background: A decrease in the nocturnal heart rate (HR) decline, nondipping HR (NHR), was reported to be 14% in the general population and related to cardiovascular events and all-cause mortality; however, the clinicopathologic features of chronic kidney disease (CKD) patients with NHR is still unclear. Previous studies have reported that interstitial and/or tubular atrophy (IT/A) was significantly associated with both daytime and nighttime hypertension observed with ambulatory blood pressure monitoring (ABPM). We aimed to investigate the clinicopathologic findings associated with NHR status in patients with CKD.

Methods: We retrospectively identified 135 subjects who underwent ABPM and kidney biopsy simultaneously at our institution, from 2016 to 2019. We excluded patients with age <20 years, end-stage kidney disease, less than 5 glomeruli in the kidney biopsy, and patients taking β-blockers. NHR status was defined as (daytime HR − nighttime HR) / daytime HR > 0.1. The percentage of global glomerulosclerosis (GS%), IT/A, and the severity of arteriosclerosis were scored semi-quantitatively according to the Mayo Clinic/Renal Pathology Society Chronicity Score (CS).

Background: Decrease in the nocturnal heart rate (HR) decline, nondipping HR (NHR), was reported to be 14% in the general population and related to cardiovascular events and all-cause mortality; however, the clinicopathologic features of chronic kidney disease (CKD) patients with NHR is still unclear. Previous studies have reported that interstitial and/or tubular atrophy (IT/A) was significantly associated with both daytime and nighttime hypertension observed with ambulatory blood pressure monitoring (ABPM). We aimed to investigate the clinicopathologic findings associated with NHR status in patients with CKD.

Results: The median age was 51 years [interquartile range: 35–63], 54.0% of which were male, and the median eGFR was 53.0 [30.0–75.0] mL/min/1.73m². NHR status was found in 39 out of 135 patients (28.9%). Patients with NHR were older and had worse renal function, higher blood pressure, lower hemoglobin level, and a larger amount of urinary protein excretion than patients with dipping HR. In terms of histopathological parameters, patients with NHR had more severe GS%, IT/A, and arteriosclerosis, and a secondary analysis excluded cardiometabolic conditions (hypertension, ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation, peripheral vascular disease, diabetes). The outcome was MACE: myocardial infarction, stroke, heart failure hospitalisation. The risk of MACE associated with number of MCCs was calculated using Cox proportional hazards models. Adjustments were made for age, sex, smoking, deprivation, eGFR and cholesterol.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Results: Of the 173,388 patients with CKD, median age was 78 years, 57% were female, 98% were of white ethnicity and median eGFR was 51.8 ± 17.3 mL/min/1.73m². There was a graded rise in the risk of MACE by MCC count (Figure 1): 1 condition adjusted hazard ratio (aHR) 1.15 (1.02-1.29), 2 MCCs aHR 1.37 (1.22-1.53), 3 MCCs 1.68 (1.50-1.88), 4+ MCCs 2.61 (2.34-2.92). For non-cardiometabolic conditions, MACE risk was lessened, but the trend persisted: 1 condition aHR 1.16 (1.12-1.20), 2 MCCs aHR 1.30 (1.25-1.35), 3 MCCs 1.43 (1.38-1.49), 4+ MCCs aHR 1.65 (1.59-1.71).

Conclusions: Patients with CKD and MCCs are at high risk of MACE, even when cardiometabolic conditions are excluded. Cardiovascular risk stratification and preventative strategies in patients with CKD should take into account the number and type of other chronic conditions.

Funding: Other NHRI Support - Medical Research Council (UK)
Turning the Page on Page Kidney with Dual RAAS Blockade
William J. AssantZA,1 Jennifer GriffithsA,1 Aromma KapoorA,1 1Westchester Medical Center Health Network, Valhalla, NY; 2New York Medical College, Valhalla, NY.

Introduction: Page kidney is a rare form of secondary hypertension from activation of the renin-angiotensin-aldosterone (RAAS) axis by compression of renal parenchyma. It can occur with blunt abdominal trauma/procedures, but it can occur spontaneously. Initial treatment is an ACE inhibitor (ACE) or angiotensin receptor blocker (ARB). Surgical intervention is necessary if more conservative measures fail. Procedures carry their own inherent risk for morbidity and mortality, particularly in the setting of uncontrolled hypertension. This report details the case of a patient with Page kidney responsive to an unconventional conservative management approach: dual RAAS blockade with ACE + ARB for a lack of response to other agents.

Case Description: The patient is a 55M with a history of end stage renal disease (ESRD) on hemodialysis (HD), atrial fibrillation, and type 2 diabetes mellitus admitted for anemia. The patient was dyspneic and weak with right flank pain. He denied hematemesis, melena, or hematuria. Hemoglobin on admission was 4.7 g/dL with INR of 4.8 (on Coumadin for atrial fibrillation). Vitals were normal except a fever to 38.4°C. A CT scan of the abdomen showed a 16.5cm right retroperitoneal hematoma adjacent to the right kidney with anterior dislocation of the kidney. A CT angiogram showed active extravasation within the hematoma. Coumadin was held and a dose of Vitamin K and two units of blood were given. The patient underwent arterial embolization. Hemoglobin was stable thereafter. The patient soon developed hypertensive urgency with blood pressure reaching 190/100 mmHg. The patient’s only home medication for blood pressure was Carvedilol. Lisinopril 20mg PO daily was added and increased to maximum dosage, only partially relieving the hypertension. Losartan was added and uptitrated to 100mg PO daily. The patient’s blood pressure normalized with average in 120s systolic by discharge. The patient was continued on this regimen as an outpatient. No hyperkalemia or hematemesis, melena, or hematuria. Hemoglobin on admission was 4.7 g/dL with INR of 4.8 (on Coumadin for atrial fibrillation). Vitals were normal except a fever to 38.4°C. A CT scan of the abdomen showed a 16.5cm right retroperitoneal hematoma adjacent to the right kidney with anterior dislocation of the kidney. A CT angiogram showed active extravasation within the hematoma. Coumadin was held and a dose of Vitamin K and two units of blood were given. The patient underwent arterial embolization. Hemoglobin was stable thereafter. The patient soon developed hypertensive urgency with blood pressure reaching 190/100 mmHg. The patient’s only home medication for blood pressure was Carvedilol. Lisinopril 20mg PO daily was added and increased to maximum dosage, only partially relieving the hypertension. Losartan was added and uptitrated to 100mg PO daily. The patient’s blood pressure normalized with average in 120s systolic by discharge. The patient was continued on this regimen as an outpatient. No hyperkalemia was observed.

Discussion: Page kidney is a rare but serious form of secondary hypertension from RAAS activation from renal parenchymal compression. Historically, a trial of either an ACE or ARB is indicated, with refractory cases being managed surgically. In this case, dual RAAS blockade was required for blood pressure control, which allowed surgical interventions, and their associated risk of morbidity and mortality, to be avoided.

ESRD Risk Predicting Using Cumulative Hypertension Burden
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Background: Hypertension is the leading risk factor for end-stage renal disease (ESRD). However, the association between sustained exposure of increased blood pressure (BP) and ESRD is not well-established. This study investigated whether the hypertension burden over a certain period for predicting the risk of ESRD from a large population-based cohort.

Methods: We retrospectively analyzed data from VHA including Veterans with ≥1 office BP measurements between January 2016 and December 2017. If more than one BP value was available, we used the lowest of the day. Prevalent hypertension was defined as diagnostic codes related to hypertension, prescribed anti-hypertensive drugs, or based on office BP values. We then evaluated the clinical variables associated with uncontrolled BP (mean BP ≥130/90 mmHg) via multivariable logistic regression with risk estimates expressed as relative risk.

Results: Of the 1,959,337 Veterans eligible for inclusion in the analysis, we found that 1,394,230 (71%) and 1,594,093 (81%) met the hypertension diagnosis criteria including ≥140/90 and ≥130/90 mmHg, respectively. Among those who met the diagnosis hypertension criteria including BP ≥140/90 mmHg (n=1,394,230), 34% (n=538,947) had controlled BP (mean BP <130/90 mmHg) and 66% (n=1,054,993) had uncontrolled BP (mean BP ≥130/90 mmHg). Older age, Black race, obesity, kidney disease, and prior cardiovascular disease (CVD) were associated with increased risk of uncontrolled hypertension (Table 1).

Conclusions: Applying the new 130/90 cut-off to the definition of hypertension increased the prevalence of hypertension by 10% in VHA. Among those with hypertension, 66% of Veterans did not meet the new BP goal of <130/90 mmHg. In addition, our findings indicate the need for targeted interventions in high-risk individuals such as Veterans with obesity, kidney disease, CVD, or of Black race.

Funding: Veterans Affairs Support

Table 1. Clinical Variables Associated with Uncontrolled Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncontrolled Hypertension (%)</th>
<th>Controlled Hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.7%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Race</td>
<td>8.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Obesity</td>
<td>8.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>CVD</td>
<td>8.4%</td>
<td>7.6%</td>
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</tbody>
</table>

Additional information: This study underlines the usefulness of a new assessment of the hypertension burden over a certain period for predicting the risk of ESRD from a large population-based cohort.
Disparities in hypertension control persist among older adults. The proportion of patients with uncontrolled hypertension by sex and by age group was calculated using marginal effects. Adjusted proportion of patients with uncontrolled hypertension by sex and by age group. Interaction term of sex*age group (<65 years, >65 years) was significant (P < 0.001) so adjusted odds of uncontrolled hypertension were calculated by sex and by age group. Adjusted proportion of patients with uncontrolled hypertension by sex and by age group was calculated using marginal effects. Results: Mean age of patients with hypertension was 64.8 ± 12.7 years; 56.3% were female, 66.6% were White, 21.4% were Black and 11.0% were of Hispanic ethnicity. Among the 5973 (27.3%) with uncontrolled hypertension, 54.7% were female; mean age was 56.2 ± 12.9 years. Adjusted odds of uncontrolled hypertension was significantly higher among women vs. men age 66-75 years (OR 1.33; 95% CI 1.30, 2.28) and age 76+ years (OR 1.73; 95% CI 1.31, 2.28) vs. age 65 years. Figure 1 shows the adjusted proportion of patients with uncontrolled hypertension by sex and by age group. Conclusions: Despite implementation of a hypertension improvement program, sex disparities in hypertension control persist among older adults.

Background: Age-dependent sex differences in hypertension control have been demonstrated in multiple populations. Four large primary care (PC) practices at Loyola adopted the Target:BP hypertension improvement program in 2018; hypertension control rates increased after adoption. Our study evaluated the impact of the Target:BP program on hypertension control by sex and by age group. Methods: Analysis used data from 21,864 patients age ≥ 18 years with a hypertension diagnosis and ≥ one outpatient visit in 2019 to a PC clinic enrolled in Target:BP program. Uncontrolled hypertension was defined as blood pressure ≥140/90 mmHg based on last visit. Mixed effects models were used to calculate adjusted odds of uncontrolled hypertension after adjustment for demographics and co-morbidities. Interaction term of sex*age group (<65 years, >65 years) was significant (P < 0.001) so adjusted odds of uncontrolled hypertension were calculated by sex and by age group. Adjusted proportion of patients with uncontrolled hypertension by sex and by age group was calculated using marginal effects. Results: Mean age of patients with hypertension was 64.8 ± 12.7 years; 56.3% were female, 66.6% were White, 21.4% were Black and 11.0% were of Hispanic ethnicity. Among the 5973 (27.3%) with uncontrolled hypertension, 54.7% were female; mean age was 56.2 ± 12.9 years. Adjusted odds of uncontrolled hypertension was significantly higher among women vs. men age 66-75 years (OR 1.33; 95% CI 1.30, 2.28) and age 76+ years (OR 1.73; 95% CI 1.31, 2.28) vs. age 65 years. Figure 1 shows the adjusted proportion of patients with uncontrolled hypertension by sex and by age group. Conclusions: Despite implementation of a hypertension improvement program, sex disparities in hypertension control persist among older adults.

Background: High potassium intake is associated with lower blood pressure and lower risk of cardiovascular disease. Whether these associations differ between men and women and whether they depend on daily sodium intake is unknown. Methods: We performed an analysis in 11,267 men and 13,696 women from the Epic-Norfolk cohort. Daily sodium and potassium consumption was estimated from sodium and potassium concentration in spot urine samples by using the Kawasaki formula. Linear and Cox regression were used to explore the association between potassium intake, systolic blood pressure and cardiovascular events (defined as hospitalization or death due to cardiovascular disease). Results: After adjustment for confounders, interaction between potassium intake and sex was significantly associated with systolic blood pressure (p = 0.001) and cardiovascular events (p = 0.035). In women, but not in men, the inverse slope between potassium intake and systolic blood pressure was steeper in those within the highest quintile compared to the lowest quintile of sodium intake (p = 0.001 for interaction). In women within the highest quintile of sodium intake, every 1-gram increase in potassium intake was associated with a 2.9 mmHg lower systolic blood pressure. These associations were paralleled with lower hazards of cardiovascular disease (highest vs. lowest potassium intake quintile: HR 0.89, 95% CI 0.83-0.95). Conversely, in men, the inverse association between potassium intake and cardiovascular disease was not statistically significant (highest vs. lowest potassium intake quintile: HR 0.94, 95% CI 0.88-1.01). Conclusions: We demonstrate that the association between potassium intake and both systolic blood pressure and cardiovascular disease is sex-specific. Our data suggests that particularly women may benefit most from a high potassium intake.
POI1775

Tryptophan Metabolites Associate with Subclinical and Incident Cardiovascular Disease in CKD
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Background: Inflammation and oxidative stress contribute to the increased cardiovascular disease (CVD) burden in CKD patients. Altered tryptophan catabolism via the kynurenine pathway associates with CVD, but the ability of these specific metabolites to act as biomarkers of CVD risk in CKD warrants further research.

Methods: We measured tryptophan metabolites using targeted mass spectrometry in moderate to severe CKD patients (n=325; median follow-up 3 years). Vascular calcification at the coronary artery and aorta was measured using a 4-slice LightSpeed QXI and reported as Agatston scores. Incident CVD events included myocardial infarction, coronary revascularization procedures, stroke, transient ischemic attack, new-onset heart failure, sudden cardiac death, and peripheral vascular disease requiring revascularization or amputation. Multiple linear regression and Cox proportional hazard analyses assessed the relationship of tryptophan metabolites to subclinical markers of CVD and CVD events.

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p=0.006). Higher baseline levels of anthranilic acid and hydroxyanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p=1.56, p=0.02 respectively). One unit decrease in serum tryptophan at baseline is associated with 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p = 0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 1.31, p=0.02 respectively), but were not significant in the fully adjusted model.

Conclusions: Lower tryptophan levels are associated with increased aortic calcification and decreased time to incident CVD events. Higher levels of anthranilic acid, hydroxyanthranilic acid, and quinolinic acid are associated with subclinical CVD. Together, these data demonstrate that catalysis of kynurenine pathway via the kynurenine pathway is associated with subclinical CVD and predicts cardiovascular events in CKD.

Funding: Other NIH Support - U2TR002240 NCATS

POI1776

Abstract Withdrawn

POI1777

High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study
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Background: The association of uromodulin and hypertension was clinically observed, but not proved as a causal relationship. We conducted a two-sample Mendelian randomization (MR) analysis to investigate the causal relationship between uromodulin and blood pressure based on the public datasets.

Methods: We selected two SNPs for the uUMOD exposure from the Genome-Wide Association Studies (GWAS) meta-analysis study(N=10884) and sixteen SNPs for uUMOD based on the open studies in Pubmed(N=4147). Six summary level studies based on the UKBiobank and ICBP served as outcomes with the sample of hypertension is 46188, a total sample size of SBP is 1194020, and the DBP is 1194025. We used the inverse variance weighted (IVW) method to combine each SNP’s effect. Three methods (IVW, MR-Egger, and Weighted median) were used to access the causal effect of serum uromodulin(uUMOD) on blood pressure. We also adopted Cochran’s Q statistic to test the heterogeneity and MR-PRESSO to confirm the horizontal pleiotropy.

Results: MR analysis of the IVW method shows uromodulin could elevate blood pressure and enhance the risk of hypertension. Odds Ratios(OR) of the uUMOD to hypertension (ukb-b-14057 and ukb-b-14117) is 1.0495% (95% Confidence Interval (CI), 1.03-1.04), while in sUMOD is 1.0195% (95% CI 1.01-1.02). Both sUMOD and uUMOD can predict the elevation of the SBP and DBP. The effect sizes of the UMOD to SBP are 1.100 and 0.028 in ieu-b-39 and ukb-b-20175 respectively. The causal relationship between uUMOD and DBP of the ieu-b-39 is 0.88g(p-value=4.3E-06) and 0.05 of the ukb-b-79292 (p-value=2.13E-10). The β coefficient of sUMOD IVW in ieu-b-38 is 0.371 and 0.011 in ukb-b-20175. For DBP in ieu-b-39 are β=0.315 (SE=0.050) and β=0.018 (SE=0.035) in ukb-b-7992.

Conclusions: Our results solidly indicated that high urinary and serum uromodulin level is a causal risk factor for hypertension.

Funding: Private Foundation Support

POI1778

Follistatin Is a Potential Novel Therapeutic Agent for Essential Hypertension
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Background: Follistatin (FST) is an inhibitor of several members of the profibrotic TGFβ superfamily. It is highly effective at neutralizing activins, without activity against TGFβ itself. Activins are known to induce inflammation, oxidative stress and fibrosis, all of which contribute to the vascular dysfunction characteristic of hypertension (HTN). We previously showed that FST inhibits kidney fibrosis, improves kidney function and lowers blood pressure (BP) in a hypertension chronic kidney disease mouse model. While this is a model of secondary HTN, here we seek to analyze the efficacy of FST in improving BP and vascular structure and function in a model of essential HTN.

Methods: Telemeters were implanted in the abdominal aorta of spontaneously hypertensive rats (SHR), a model of essential HTN, and normotensive control Wistar Kyoto (WKY) rats for wireless BP monitoring. Rats were treated with 0.075mg/kg FST or vehicle IP every other day from 12-20 weeks of age (8 weeks). BP was recorded weekly. First branch mesenteric arteries were harvested for analysis of vascular function using myography, assessed for oxidative stress by DHE, or formalin fixed for IHC.

Results: By the end of the study, FST significantly lowered both systolic and diastolic BP in SHRs (200 ±9.9 over 132 ±4.3 mmHg in control and 189 ±2.2 over 123 ±2.2 mmHg in FST-treated SHRs, P < 0.04 and P < 0.03 respectively). SHR vessels showed increased contractility with the a1 adrenergic agonist phenylephrine, which was attenuated by FST. Post-hoc analyses demonstrated a decrease in myogenic-dependent relaxation in SHR vessels was also improved by FST. Structurally, FST-treated vessels had less collagen deposition, assessed by Trichrome, which was accompanied by a reduction in medial thickness. Increased oxidative stress seen in SHR vessels was inhibited by FST.

Conclusions: FST lowers BP in SHR with established HTN, at least in part by reducing vascular oxidative stress and medial thickening. This manifests as improved vascular function, with decreased hypersensitivity to contractile agents and improved endothelial function. Future work will identify the effects of FST on inflammation, and the role of specific activins in essential HTN.

Funding: Private Foundation Support

POI1779

Age and Sex Disparities in Hypertension Treatment Inertia After Implementation of Target: BP
Olivea Myers,1 Talar Markossian,1 Beatrice D. Probst,2 Katherine Habich,2 Holly J. Kramer.1 Loyola University Chicago, Chicago, IL; 2Loyola University Health System, Maywood, IL.

Background: Blood pressure (BP) control decreases with advancing age among women but not men, but reasons for sex disparities remain uncertain. Our institution enrolled four large outpatient primary care clinics in the Target:BP hypertension improvement program in 2018. This hypertension improvement program included audit and feedback of physician prescribing practices of BP lowering medications. We examined the adjusted association of medication escalation, a measure of treatment inertia, with age group among adults with uncontrolled hypertension and determined whether this association is modified by sex. We hypothesized that medication escalation for BP control differs by age group and by sex.

Methods: Adults age 18 years with uncontrolled hypertension (BP ≥ 140/90 mmHg at last visit) receiving primary care at a clinic enrolled in Target:BP and a 1 primary care visit during 2019 were included. Medication escalation was defined as a change in BP lowering medication class or dose during a visit when hypertension was uncontrolled. Mixed effects models were used to calculate adjusted odds of medication escalation by age group (≤ 65, 66-75, ≥ 76 years) after adjustment for demographics and co-morbidities. Interaction term of sex by age group was then fitted in fully adjusted mixed effects models and was significant (P < 0.001). Adjusted odds of medication escalation were then calculated by sex and by age group and adjusted prevalence of medication escalation by age group and by sex was calculated using marginal effects.

Results: Mean age of 5973 adults with uncontrolled hypertension was 65.2 (SD 5.2) years; 54.7% were women; 64.7% were White, 24.0% were Black and 9.9% were Hispanic ethnicity. Figure (left panel) shows that adjusted prevalence of medication escalation declined with advancing age group among men and women combined. Right panel shows the decline in medication escalation with advancing age group differed by sex until age 76+ years.

Conclusions: Medication escalation for uncontrolled hypertension declines with advancing age and this age associated treatment inertia differs by sex.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

550
PO1780
Oscillometric vs. Auscultatory Blood Pressure Measurements and the Impact of Atrial Fibrillation
Ahmed Abrahama, Christopher B. McFadden. Cooper University Health Care, Camden, NJ.

Background: The Hypertension literature recognizes a difference in Oscillometric Blood pressures compared to Auscultatory Blood pressure measurements. These differences are small but increased in patients with Atrial fibrillation. This difference varies in previous studies. Again this Difference is larger in subjects with atrial fibrillation. Current Blood pressure measurement guidelines emphasize the use of an Auscultatory method or repeated oscillometric measures to measure blood pressure in patient with arrhythmias including atrial fibrillation. This recommendation is not consistently implemented in clinical medicine. We aim to quantify the differences in blood pressure readings between oscillometric and auscultatory method and correlate that to presence or absence of atrial fibrillation.

Methods: This is a retrospective study that involved adult patients seen in the outpatient nephrology clinic by one of the investigators (CM) between January 2016 and January 2020. Data collection included age, sex, BMI, atrial fibrillation (AF), CKD stage, diabetes mellitus, blood pressure readings (by both methods, which were done by the investigator (CM) in all antihypertensive patients) and number of blood pressure medications. Information on a total of 200 patients were collected. 100 of those had hypertension with AF while the other 100 had hypertension but no AF to achieve a power of 80% and P value of 0.05.

Results: After using Unpaired t test, the average difference between two methods in hypertensive patients with atrial fibrillation was 0.9±1.29 mmHg in systolic blood pressure (P value of 0.9 and 95% CI from -5.5 to 6.12) and 5.39 mmHg in diastolic blood pressure (P value of 0.0068 and 95% CI from 1.5 to 9.24). On the other hand, the average difference between two methods in hypertensive patients with atrial fibrillation were 6.8 mmHg in systolic blood pressure (P value of 0.018 and 95% CI from 1.18 to 12.5) and 5.04 mmHg in diastolic blood pressure (P value of 0.002 and 95% CI from 1.87 to 8.21).

Conclusions: This study showed a statistical difference between the two methods in measuring the blood pressure of hypertensive patients with atrial fibrillation. A larger study is needed to show no difference between the two methods. For now we need to encourage the use of auscultatory method in measuring the Blood pressure in this group of patients.

PO1781
Single-Nephron Salt Excretion and Nighttime Hypertension: A Cross-Sectional Study in Patients with IgA Nephropathy
Nobu Tsuibo, Hirokazu Marumoto, Kotaro Harahara, Takaya Sasaki, Yusuke Okabayashi, Go Kanzaki, Kentaro Koike, Takashi Yokoo. Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan, Tokyo, Japan.

Background: Abnormalities in diurnal blood pressure variability and renal salt handling may contribute to poor disease outcomes in patients with IgA nephropathy (IgAN). This study examined the relationships between diurnal blood pressure variability and single-nephron urinary salt excretion (SNUSE) in IgAN patients.

Methods: The subjects were IgAN patients who underwent ambulatory blood pressure (ABP) monitoring and 24-h urine collection during hospitalization for a diagnostic biopsy. In all patients, dietary salt intake was restricted to 6 g/day during hospitalization. Daytime and nighttime hypertension were defined as daytime ABP ≥ 135/85 mmHg and nighttime ABP ≥120/70 mmHg, respectively. The total nephron number per kidney was estimated by a combined cortical volume assessment of unenhanced computed tomography images and stereology-based measurements of non-sclerotic glomerular density in a biopsy. SNUSE was calculated by dividing urinary salt excretion per day by the total nephron number of both kidneys.

Results: Among the 112 patients (42 years old, 63.4% male, estimated glomerular filtration rate [GFR] 62.4 mL/min/1.73 m²) included, daytime and nighttime hypertension were noted in 33.0% and 50.9%, respectively. There was no marked difference in the total nephron number or SNUSE in relation to the daytime hypertension. In patients with nighttime hypertension, the total nephron number per kidney was lower (490,000 vs. 796,000/kidney, p = 0.01) and SNUSE was higher (6.53 vs. 4.22 µg/day, p =0.003) than in normotensive patients during nighttime. An increase in SNUSE in patients with nighttime hypertension was associated with advanced tubulointerstitial injury, defined as a T score in the Oxford histopathological classification of IgAN. The single-nephron GFR was comparable among groups with and without hypertension both during the daytime and nighttime and was not associated with a T score.

Conclusions: These results provide evidence that salt excretion per nephron is increased in IgAN patients presenting with nighttime hypertension. The difference in SNUSE was identified in relation to the tubulointerstitial injury without producing a difference in single-nephron GFR values among ABP categories, indicating compensatory changes in tubular salt handling at the single-nephron level.

Funding: Other U.S. Government Support

PO1782
Small Changes in eGFR Are Associated with Different Patterns of 24-Hour Ambulatory Blood Pressure Monitoring in the General Population
Sang Youn Han, Sanggyoon Yoon, Seung Ku Lee, Chol Shin. Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea.

Background: Alteration of circadian blood pressure (BP) rhythm such as non-dipper and reverse dipper pattern is associated with cardiovascular diseases and chronic kidney disease (CKD). However, most studies did not control for kidney function even though kidney function is an important risk factor. In this study, we tried to show 24-h ambulatory blood pressure monitoring (ABPM) patterns based on an eGFR in patients without CKD.

Methods: This study was a cross-sectional study from the data of the Korean Genome and Epidemiology Study, which is ongoing prospective cohort study. A total of 1733 participants (60.0±7.0 years, 938 women) who had an eGFR > 60 ml/min/1.73m² were included. Dipping status was stratified as reverse dipper (≥40%), non-dipper (0% to <40%), and dipper (≥10%) based on the night to day ratio of mean BP. They were divided into 4 groups based on quartile of an eGFR (Q4, 128.6-101.6; Q3, 101.5-95.7; Q2, 95.6-87.4; Q1, 87.3-60.5).

Results: The proportion of dipper was progressively decreased from the highest to the lowest eGFR whereas that of reverse dipper and non-dipper significantly increased. (P<0.001). We analyzed the data using logistic regression model in relation to dipper, non- dipper, reverse dipper, and non-dipper plus reverse dipper according to the quartiles of an eGFR. The highest quartile group (Q4) was fixed as the reference. In univariate analyses, Q1 and Q2 groups were significantly associated with increasing odds ratio (OR) with increased reverse dipper, non-dipper plus reverse dipper. After full-adjustment with age, sex, hypertension, diabetes, body mass index, smoking status, exercise, and alcohol consumption, the lowest eGFR group was significantly associated with reverse dippers and non-dipper plus reverse dippers compared to the highest eGFR group (OR=1.689, 95% CI, 1.005-2.840; OR=1.427, 95% CI, 1.027-1.895, respectively). The significant linear trend of non-dipper plus reverse dipper with a decrease in eGFR was confirmed with the test for trend (P=0.024).

Conclusions: Small changes in eGFR are associated with different pattern of 24-h Ambulatory blood pressure in general population. ABPM could be useful tool to detect patients with non- dipper in this population.

Funding: Other U.S. Government Support
PO1784

Crit-Line Monitoring Effect on Blood Pressure Control in ESRD Patients Undergoing In-Center Hemodialysis
Maggie Meier, Hassan Ifikhar, Alexandra Y. Li, Frank J. O Brien. Washington University in St Louis, St Louis, MO.

Background: Patients with end stage renal disease (ESRD) are admitted to the hospital about twice per year, with a 35% readmission rate. Cardiovascular disease (CVD) makes up 28% of admissions, 38% of patients with CVD admissions have pneumonia edema. Fluid overload in ESRD increases morbidity and mortality. Fluid management improvements have potential to positively impact clinic outcomes in dialysis patients.

Methods: This was a prospective cohort study with adult patients at two outpatient dialysis facilities on the Washington University in St Louis Campus. Our inclusion criteria were patients with consistent 3x weekly in center hemodialysis defined as 80% attendance in the 30 days prior to the study. A critline protocol was implemented by the treatment team (Figure 1).

Results: Among 58 qualified patients, average age was 59. 77% were African American with male predominance (57%). Average BMI was 29. In the Critline cohort, systolic blood pressure trended down (Figure 2). In the initial 25 weeks, average number of antihypertensive medications per patient decreased from 2.6 to 1.8. The number of admissions for fluid overload stayed at stable, however readmissions decreased from 4 to 1.

Conclusions: Implementing a Critline protocol trended towards improvements in blood pressure and reduced number of antihypertensives medications. Our findings suggest that a protocolized approach to fluid management using critline will improve our patients outcomes.

PO1785

Cardiovascular Functional Changes in Transplant Waitlist Dialysis Patients
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Background: The transition to dialysis is a crucial time in patients with advanced chronic kidney disease (CKD), conferring an increased risk for cardiovascular death. We recently showed that VO,Pek, an index of cardiovascular functional capacity (CFC) significantly declined in advanced CKD patients following 1-year follow-up in the absence of changes in left ventricular mass index (LVMI). Herein, we hypothesized that initiating dialysis and continuing dialysis could worsen an individual’s CFC over time.

Methods: We conducted a cross-sectional study of 241 CKD stage 5 patients from the Cardiopulmonary Exercise Testing in Renal Failure (CAPER) cohort. VO,Pek (primary endpoint) was assessed by cardiopulmonary exercise testing (CPET) in parallel with transthoracic echocardiography.

Results: Of the 241 patients (mean age [SD] age, 48.9 [14.9] years; 154 [65.9%] male), 77% were predialysis (mean eGFR [SD], 14 [3.4] ml/min/1.73m²). Major 78% were in tertile 1 of dialysis vintage (0-17 months), n=69 in tertile 2 (18-50 months) and n=64 in tertile 3 (≥51 months). Predialysis patients had an impaired VO,Pek of 22.7 [5.2] ml/min/kg, and this significantly declined to 18.5 [5.5] ml/min/kg in tertile 1 dialysis patients compared to the pre-dialysis group, tertile 1 dialysis patients exhibited reduced maximal workload (p=0.003), impaired maximal heart rate (p=0.02), increased LVM (p=0.001) and markedly elevated FGF23 levels (p=0.01). On assessment of the effects of dialysis vintage, we found an incremental downward trend in VO,Pek across the groups (22.7 [5.2] tertile 1, 18.4 [4.7] tertile 2, 16.9 [4.2] ml/min/kg) following exclusion of patients who had prior kidney transplants, however this did not reach statistical significance (p=0.2).

Conclusions: Initiating dialysis in advanced CKD patients is associated with impaired CFC comparable to declines seen in new onset heart failure, making this a critical time for these patients.

PO1786

Major Adverse Limb Events and Mortality After Peripheral Artery Revascularization in Hemodialysis Patients
Ting-yan Lin, Shu-Chun Hung. Taipei Tzu Chi Hospital, Taipei, Taiwan.

Background: Revascularization is important for symptom relief and limb salvage in peripheral artery disease, yet limited information exists on the prognosis of hemodialysis patients who receive the procedure. This study sought to determine the incidence and associated factors of major adverse limb events (MALE) after peripheral artery revascularization among hemodialysis patients.

Methods: Hemodialysis patients undergoing peripheral artery revascularization between July 1, 2005, and December 31, 2019, in the Taipei Tzu Chi Hospital were examined for the primary outcome of MALE, defined as severe limb ischemia leading to an intervention or amputation. The secondary outcomes included major adverse cardiovascular events (MACE) and all-cause mortality. Multivariable-adjusted Cox proportional hazards models were used to explore risk factors associated with development of MALE.

Results: A total of 402 hemodialysis patients were included in the final analysis. Overall, the mean age was 68 years, 56.5% (n = 227) were male, 83.3% (n = 335) had diabetes, and 58.0% (n = 213) had coronary artery disease. During a median follow-up of 2.2 years, 54.0% (n = 217) experienced a subsequent MALE, 33.6% (n = 136) had a MACE, and 54.5% (n = 219) died. Diabetes, coronary artery disease, current smoking, lower body mass index, and higher platelet count or total cholesterol were significantly associated with increased risk of post-procedure MALE.

Conclusions: A significant proportion of hemodialysis patients undergoing peripheral artery revascularization developed a subsequent MALE and MACE or died. Strategies that address risk factors for MALE should be evaluated to improve the outcomes of revascularized hemodialysis patients.

PO1787

Central Blood Pressure Calibration Method and Cardiovascular Risk Prediction According to Sex
Florence Lamarche1, Mohsen Agharazi3, Annie-Claire Nadeau-Fredette,7 Francois Madore1, Remi Goupil.1 Hôpital du Sacre-Coeur de Montreal, Montreal, QC, Canada; 2Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 3CHU de Quebec-Universite Laval, Quebec, QC, Canada.

Background: The accuracy of central BP is improved when calibrated on the mean BP and diastolic BP (C2SBP) compared to calibration on the systolic BP and diastolic BP (C1SBP). Furthermore, preliminary data suggest C2SBP may have the best accuracy in females. We aim to assess whether this enhanced accuracy translates into improved cardiovascular (CV) risk prediction when compared to brachial SBP (bSBP) and C1SBP in the general population and stratified by sex.

Methods: 12,927 participants exempt of known CV disease, with prospective follow-up from administrative databases and central BP measurements, were included. The SphygmoCor Px device was used to estimate C1SBP. C2SBP was derived from unprocessed radial pressure waveforms extracted from SphygmoCor output data, which was recalibrated with diastolic BP and 40% form factor derived mean BP. Participants with heart rate <60 were excluded due to incomplete waveforms. Major adverse CV events (MACE) comprised myocardial infarction, stroke, heart failure with hospitalization and CV death. Multivariable Cox regressions, differences in area under the curve, net reclassification index and integrated discrimination index were calculated comparing C2SBP to C1SBP and to bSBP.

Results: Over a median follow-up of 10.1 years (IQR 9.9-10.3), there were 2125 MACE (723/7013 females and 860/5934 males). All BP parameters were significantly associated with MACE, regardless of sex. In the overall cohort, risk prediction metrics marginally favored C2SBP compared to bSBP, but were similar to C1SBP. No significant improvement of CV risk prediction was found in sex-stratified analyses (see Table).

Conclusions: C2SBP marginally improved CV risk prediction when compared to bSBP but not C1SBP in the overall cohort only. All three BP parameters were similarly predictive in both sex, although this analysis possibly lacked power. This may be related to the FP-derived MAP (rather than oscillometric MAP), which is highly dependent on the brachial SBP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PO1788
Suppressed Renin Activity in CKD: Are We Missing Primary Hyperaldosteronism?

Methods:
We reviewed patients in the Cleveland Clinic CKD registry with documented PRA and absolute plasma aldosterone concentration (PAC). Patients in the lowest PRA quartile were identified and stratified by PAC/PRA ratio. A cutoff ratio of ≥20 was considered suggestive of PA regardless of the PAC. Characteristics and outcomes of these two subgroups were compared using t-tests, chi-square tests, Kaplan-Meier analyses and Cox models.

Results:
276 patients were identified for this analysis. Median PRA and PAC were 0.5 µg/L/hr and 8.7 ng/dl, respectively. 141 (51%) patients had a PAC/PRA ratio of ≥20 with a median PAC of 14.6 ng/dl in this subgroup. Patients with PAC/PRA of ≥20 had significantly lower eGFR than patients with PAC/PRA of <20 (mean: 50.7 vs. 55.4, p<0.001), more resistant hypertension (63.1% vs. 48.9%, p=0.044), lower serum potassium values (mean: 3.9 vs. 4.2 mmol/L; p<0.001), and higher serum bicarbonate levels (mean: 26.4 vs. 25.3 mmol/L; p=0.001). With median follow up of 4.2 years, there was no difference in mortality between the two subgroups on adjusted cox model analysis (HR for ≥20 vs.<20: 1.03, 95% CI: 0.61-1.74). There was no difference in ESKD-free survival at 5 years was noted but the event rate was low (92.6 vs. 91.9 for ≥20 vs.<20; p=0.77).

Conclusions: We hypothesized that some of these patients with suppressed PRA may have undiagnosed PA. More than half of our suppressed PRA cohort had elevated PAC/PRA ratio suggestive of PA. The biochemical profile and severe hypertension further support the diagnosis. We hypothesize that the diagnosis of PA was possibly ruled out because of the “not very high” PAC. Given the limitations of the spot PAC/PRA screen owing to diurnal PAC variations, a suppressed PRA should merit an in-depth evaluation for undiagnosed PA regardless of the PAC. Making this diagnosis is critical since it has significant therapeutic implications.

PO1790
Cardiovascular and Renal Outcomes of the New Intensive Blood Pressure Target in a CKD Population in Korea

Methods:
The data of 166,397 adults whose baseline estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m² were extracted from the Korean National Health Insurance Service database between 2009 and 2011. The data were adjusted for multiple factors such as age, sex, smoking, eGFR, and anti-hypertensive medications in multivariate Cox proportional hazards regression models. All participants were divided into four SBP categories (<120 mmHg, 120-129 mmHg, 130-139 mmHg, ≥140 mmHg). The primary outcome was CVD risk, and the secondary outcome was the risk of progression to end-stage renal disease (ESRD), especially in need of intermittent hemodialysis (HD).

Results:
The mean ages of the each group of CKD patients were 45.1±15.7 years in SBP <120 mmHg group and 52.1±16.0 years in SBP 120-129 mmHg group. 11.1% in SBP <120 mmHg group and 24.6% in SBP 120-129 mmHg group of the participants were already taking anti-hypertensive medications. 112,012 patients (67.3%) had SBP ≥120 mmHg, and 78,119 patients (46.9%) had SBP ≥130 mmHg. Participants with SBP ≥120-129 mmHg exhibited a significantly high risk for HD (hazard ratio (HR), 1.29; 95% confidence interval (CI), 1.03-1.61; P<0.05) and stroke (HR, 1.57; 95% CI, 1.13-2.18; P<0.01) compared with the participants with SBP <120 mmHg. Also, the risk of progression to ESRD was also higher (HR, 1.67; 95% CI, 1.46-1.91; P<0.001).

Conclusions: Therefore, the new intensive BP target can be applied to the real clinical practice in CKD population with proper BP monitoring in Korea and it may eventually reduce the risk of CVD and progression to ESRD in a number of CKD outpatients.

PO1791
Intensive Blood Pressure Control, Age, and All-Cause Mortality in the US Veterans Health Administration

Methods:
We retrospectively analyzed a Veterans Health Administration (VHA) database included Veterans with ≥2 systolic blood pressure (SBP) readings between January 2016 and December 2017 excluding those with mean SBP <100 mmHg to minimize reverse causation. Pevlant hypertension was defined as diagnostic codes related to hypertension, prescribed antihypertensive drugs, or ≥2 office BP of ≥130 mmHg. Of the 1,959,003 Veterans, 18% had SBP <120 mmHg (n=352,684), 26% had SBP 120-129 mmHg (n=507,907), and 56% had SBP >130 mmHg (n=1,091,412)

Results:
The estimated effect of SBP control on all-cause mortality and evaluated the potential interaction with age using a random-effect Cox regression model.

Conclusions: Intensive blood pressure (BP) control has been shown to improve survival in large clinical trials. It is unknown if intensive BP control is associated with improved outcomes amongst older adults in the real-world setting. We examined the association of intensive BP control with all-cause mortality in U.S. Veterans.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Markers of Kidney Tubular Secretion and Risk of Cardiovascular Disease and Mortality in Persons with CKD in SPRINT
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Jesse C. Seegmiller,1 Joachim H. Ix,6 Michael Shlipak,1 Pranav S. Garimella,1
Kidney Health Research Collaborative, Department of Medicine, San Francisco Veterans Affairs Health Care System and University of California San Francisco, San Francisco, CA; 2University of California Davis, Davis, CA; 3University of Washington, Seattle, WA; 4University of California San Diego, La Jolla, CA, US, academic, La Jolla, CA; 5University of California San Diego, San Diego, CA; 6University of Minnesota Academic Health Center, Minneapolis, MN; 7Veterans Affairs San Diego Healthcare System, San Diego, CA.

Background: Tubular secretion of organic solutes is essential to the clearance of many drugs, metabolites, and toxins. Whether novel measures of tubular secretion have prognostic value for cardiovascular and mortality risk among hypertensive, non-diabetic persons with CKD is uncertain.

Methods: In 2089 SPRINT (Systolic Blood Pressure Intervention Trial) participants with baseline eGFR <60 ml/min/1.73m2, we created a summary secretion score from 10 tubular secretion biomarkers by averaging across their urine-to-plasma ratios. We used multivariable Cox proportional hazards models to evaluate associations between secretion scores and risk of cardiovascular disease (CVD) and all-cause mortality.

Results: Mean age at baseline was 73 ± 9 years and mean eGFR was 46 ± 11 ml/min/1.73m2. There were 272 CVD events and 144 deaths during a median follow-up of 3.2 years. In unadjusted analyses, a 1-SD higher secretion score was associated with a lower risk of CVD (hazard ratio [HR] per 1-SD higher secretion score: 0.87; 95% CI: 0.76, 0.99), but not all-cause mortality (HR: 0.95, 95% CI: 0.80, 1.13) (Table). After additionally adjusting for baseline eGFR and albuminuria, the association attenuated and was no longer significant (HR: 1.01, 95% CI: 0.67, 1.50). In multivariable analyses of the individual AEs, higher secretion was independently associated with higher risk of syncope or hypotension (HR per 1-SD higher secretion score: 1.30, 95% CI: 1.10, 1.54) and lower risk of ambulatory hypokalemia (HR: 0.71, 95% CI: 0.54, 0.95).

Conclusions: Among SPRINT participants with CKD, higher tubular secretion was not significantly associated with risk of CVD or mortality after adjustment for eGFR and albuminuria.

Funding: NIDDK Support

POI1796

Associations of CKD with Dementia Before and After Transient Ischemic Attack and Stroke in a Population-Based Cohort Study


Background: Individuals with chronic kidney disease (CKD) appear to have a greater risk of developing cognitive disorders than the general population. Both vascular and neurodegenerative hypotheses have been proposed to underlie this cognitive burden.

To explore the vascular hypothesis further, we investigated the association between CKD and dementia before and after transient ischaemic attack (TIA) and stroke.

Methods: In a prospective, population-based cohort study of TIA and stroke (Oxford Vascular Study; 2002-2012), pre-event and new post-event dementia were ascertained through direct patient assessment and follow-up for 5 years, supplemented by review of hospital/primary care records. Associations between pre-dementia and CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²) were examined using logistic regression, and between post-event dementia and CKD using both Cox and competing risk regression models, adjusted for age, sex, education, cerebrovascular burden (stroke severity, prior stroke, white matter disease), diabetes mellitus, and dyslipidaemia.

Results: Among 2305 TIA/stroke patients (median [IQR] age, 77 [67-84] years, 1174 [51%] male, 688 [30%] TIA), 1174 (50.9%) had CKD. CKD initially appeared to be associated with both pre-event (odds ratio [OR], 2.04 [95% CI, 1.52-2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI, 1.65-2.44]; P=0.001); however, these associations attenuated and became non-significant after adjustment for the above covariates (OR=0.92 [0.65-1.31]; P=0.65 and HR=1.09 [0.85-1.39]; P=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43-2.12]; P<0.001, attenuating to 1.01 [0.78-1.33]; P=0.92 with complete adjustment).

CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70-3.17; P<0.001), particularly in the minor events subgroup (SHR=3.08, 2.05-4.64; P=0.001), but not significantly so after complete adjustment (SHR=1.53, 0.90-2.60; P=0.12).

Conclusions: In patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that age, sex, education, and cerebrovascular burden may play a more important role in the relationship than renal-specific neurodegenerative mechanisms.

POI1795

Carotid Plaque Characteristics and Incident Cognitive Impairment in Hypertensive Adults

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Background: Carotid atherosclerosis is associated with cognitive impairment. We investigated associations of plaque characteristics on carotid magnetic resonance imaging (MRI) with the development of mild cognitive impairment (MCI) or probable dementia.

Methods: In an ancillary study to the Systolic Blood Pressure Intervention Trial (SPRINT), carotid plaque was identified by MRI and characterized as having a lipid-rich necrotic core (NC) or calcification. In the parent study, adjudicated MCI and probable dementia were adjudicated on the basis of neuropsychological testing and proxy reports of cognitive-related decline in functional status. We related baseline plaque presence and characteristics of NC or calcification with the incidence of MCI/probable dementia at 3 years of follow-up.

Results: Of 465 participants, 137 (29.5%) had NC plaque. Those with NC plaque were older and more likely to have cardiovascular disease than those without NC plaque. There were 38 MCI/probable dementia outcomes in the entire cohort over 2220 person-years of follow-up. The incidence (95% CI) of a composite outcome of MCI or probable dementia at 3 years was 12.0% (7.5, 18.9) in the NC group and 7.0% (4.6, 10.4) in the no NC group with an absolute risk difference of 5.1% (95% CI -1.2, 11.3, P=0.11). With further adjustment, the absolute risk difference attenuated but the point estimate remained significant (Figure). Results for the presence of any plaque or calcified plaque with MCI/probable dementia are also summarized in the Figure.

Conclusions: We observed large differences in risk for MCI/probable dementia associated with the presence vs. absence of NC plaques, but the significance of this finding is uncertain due to the small number of incident cases of cognitive impairment. Nonetheless, our observations indicate the need to study NC plaque as a novel and potentially more relevant marker of vascular health in future studies of cognitive impairment in hypertensive adults.

Funding: NIDDK Support, Veterans Affairs Support
PO1798
Platelet Activity Mediates Enhanced Cardiovascular Risk in Patients with CKD and Peripheral Artery Disease

Background: Chronic kidney disease (CKD) is common in patients with peripheral artery disease (PAD), and both are associated with poor cardiovascular (CV) outcomes. Platelets drive PAD pathogenesis and mediate atherosclerosis. Platelet function in CKD and the related CV risk is unclear. We investigated relationships between CKD, platelet activity, and incident CV events in a cohort of patients with PAD.

Methods: The Platelet Activity and Cardiovascular Events (PACE) study enrolled 289 patients with PAD undergoing lower extremity revascularization (LER). CKD was defined as eGFR<60 mL/min/1.73m² by the CKD-EPI equation. We measured platelet activity via light transmission aggregometry (LTA) in response to submaximal ADP, serotonin, epinephrine, and arachidonic acid (AA) prior to LER, and followed patients for a median of 18 months. The primary clinical endpoints were myocardial infarction (MI) and a composite of major adverse CV events (MACE; MI, stroke, death).

Results: There were 113 (40%) patients with and 172 (60%) without CKD. Patients with CKD (vs. non-CKD) were older and more likely to be female, Hispanic, have diabetes, heart failure, and critical limb ischemia (P<0.05 for each). There were no significant differences in prevalent coronary artery disease or use of antithrombolytic therapy between groups. Platelet aggregation in response to submaximal ADP, serotonin, epinephrine, and AA was elevated in the CKD group (Figure). After multivariable adjustment, patients with CKD were at greater risk of MI (aHR 2.2 [95% CI: 1.02–4.9]; P=0.045) and MACE (aHR 1.9 [1.2–3.3]; P=0.01). Patients with CKD were also associated with an increased risk of incident CV events and cardiac events in HD patients. Our results indicate that VAP-1 helps clinicians identify those at high risk of CV events.

Conclusions: Plasma VAP-1 levels had the positive relationship with circulating levels of neprilysin and RAS activity and LV diastolic dysfunction. Higher VAP-1 levels were also associated with an increased risk of incident CV events and cardiac events in HD patients. We investigated relationships between CKD and the risk of incident CV events in a cohort of patients with PAD. Our results indicate that VAP-1 helps clinicians identify those at high risk of CV events.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Kidney Function Trajectory Following Left Ventricular Assist Device Implantation

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Background: LVADs have variable effects on kidney function. Identification of distinctive eGFR trajectory groups after LVAD placement, by applying unsupervised techniques to longitudinal eGFR measures, may enable insights into diverse pathophysiology.

Methods: From a national cohort, we identified persons who underwent isolated, primary continuous flow LVAD implantation in the US, 2016-17. eGFR values from pre-LVAD implantation to 12 months post were used. Latent class mixed models using cubic splines were applied to derivation and validation subsets, and models with 2-9 distinct groups were evaluated to find the optimal number.

Results: In the cohort (3,461 in derivation subset, 1,154 in validation), we identified 5 distinct trajectory groups. The 2 largest groups (1,2) are similar to previously reported cohort averages, with early eGFR increase followed by decline, but differed by baseline eGFR. Three smaller groups (3-5, ~15% of the cohort) demonstrated novel trajectories: group 3 had early worsening with sustained low kidney function; 4 had early and sustained eGFR improvement, and 5 had substantial eGFR variation. These groups differed in baseline factors (groups 3 and 4 had the most pre-LVAD acute dialysis, 4 and 5 the most cardiogenic shock) and outcomes (groups 2 and 4 had the highest survival, 3 and 5 had the lowest).

Conclusions: Novel eGFR trajectories after LVAD implantation were identified in a national cohort. Group 4, with early and sustained increase in eGFR, may reflect type 1 cardiorenal syndrome. Group 3 may reflect chronic kidney disease with early complications, and group 5 may reflect intact kidney parenchyma but post-LVAD right ventricular failure. These results demonstrate the feasibility of identifying previously unobserved heterogeneity in kidney outcomes. The novel trajectory groups may reveal potential for tailored care, in addition to pathophysiologic insights.

Funding: NIDDK Support

Diuretic Resistance in Acute Decompensated Heart Failure with Preserved vs. Reduced Ejection Fraction

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Background: Loop diuretics are one of the common causes of inadequate decongestion in patients hospitalized with acute decompensated heart failure (ADHF). However, DR has not been characterized in patients with HF with preserved ejection fraction (HFpEF).

Methods: In a post hoc analysis of a pilot study which evaluated the role of high-dose spironolactone in hospitalized ADHF patients with DR, we analyzed the prevalence and potential pathophysiologic factors of DR in HFpEF (n=20), and compared those with HF with reduced EF (HFrEF) (n=27). DR was defined as weight loss<1lb/day despite intravenous furosemide>160mg/day (at least one dose of 80mg/day) or no change in urine sodium/potassium ratio, plasma renin activity and aldosterone were lower in DR-HFpEF as compared to DR-HFrEF, though still higher than diuretic responsive-HFpEF patients (Table 1). Weight loss in response to high-dose spironolactone was similar in DR-HFpEF and HFpEF (14±8.6 vs.14±13 lb).

Results: DR was observed in 10 (50%) of HFpEF subjects as compared to 10 (37%) of HFrEF subjects (p=ns). In general, patients with HFpEF were older, more female and obese, had more diabetes, higher systolic blood pressure and lower brain natriuretic peptide compared to HFrEF (Table 1). There was no difference in clinical presentation, eGFR and pulmonary arterial systolic pressure in DR-HFpEF vs. DR-HFrEF. However, urine sodium/potassium ratio, plasma renin activity and aldosterone were lower in DR-HFpEF as compared to DR-HFrEF, though still higher than diuretic responsive-HFpEF patients (Table 1).

Funding: NIDDK Support
Conclusions: Although the comparisons were not statistically significant due to small sample size; the results suggest that DR is more prevalent in HfPEF. Despite similar clinical features of congestion and response to high-dose spironolactone, a state of reduced neurohormonal activation points that additional factors might be contributing to DR in HfPEF compared to HFrEF patients.

Funding: Commercial Support - Relypsa Education Grant

Table 1: Baseline characteristics of HFrEF vs. HfPEF patients

<table>
<thead>
<tr>
<th></th>
<th>HFrEF</th>
<th>HfPEF</th>
<th>p-value</th>
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<tr>
<td>Age</td>
<td>55 (1.1)</td>
<td>55 (1.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>80/20</td>
<td>80/20</td>
<td>0.36</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>28.7 (6.3)</td>
<td>28.7 (6.3)</td>
<td>0.98</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129 (20.7)</td>
<td>115 (18.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78 (13.3)</td>
<td>76 (11.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>PVR (%)</td>
<td>62.9</td>
<td>62.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Deterioration (CVD)</td>
<td>39/60</td>
<td>39/60</td>
<td>1.00</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>60 (24)</td>
<td>60 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>Creatinine &amp; proteinuria</td>
<td>0.1 (0.01)</td>
<td>0.1 (0.01)</td>
<td>1.00</td>
</tr>
<tr>
<td>PFT</td>
<td>43 (10.0)</td>
<td>45 (9.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Brain natriuretic peptide (BNP) (pg/mL)</td>
<td>2.20 (13.4)</td>
<td>2.20 (13.4)</td>
<td>1.00</td>
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<tr>
<td>Albuminarn (g/dL)</td>
<td>2.6 (0.5)</td>
<td>2.6 (0.5)</td>
<td>0.72</td>
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<tr>
<td>Erythropoietin (pg/mL)</td>
<td>6.3</td>
<td>6.3</td>
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<tr>
<td>Before (mg/24h)</td>
<td>195 (179)</td>
<td>195 (179)</td>
<td>1.00</td>
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<tr>
<td>After (mg/24h)</td>
<td>195 (179)</td>
<td>195 (179)</td>
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**Table 1:** Comparison of Baseline Characteristics between HFrEF and HfPEF patients.

**PO1805**

Renal Outcomes and Safety of Angiotensin Receptor Neprilysin Inhibitors in Patients with Heart Failure: A Meta-Analysis

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Background: Angiotensin receptor neprilysin inhibitors (ARNIs) are an effective treatment for heart failure. However, their safety profile compared with angiotensin converting enzyme-inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with respect to renal outcomes has not been clearly established.

Methods: We conducted a literature search of MEDLINE, Cochrane library, Embase, and clinical trials registries using relevant search terms (last search date May 7, 2021). The primary renal outcome was kidney function decline and the safety outcome was hyperkalemia. Only studies with at least 12 weeks of follow up were included in the renal outcome analysis to better capture CKD.

Results: Ten randomized controlled trials were eligible for inclusion (n=22,174 participants). ARNIs were associated with a lower risk of kidney function decline compared with ACEIs or ARBs: RR 0.65 (95%CI 0.53-0.81). The risk of hyperkalemia was similar in both treatment groups: RR 0.96 (95%CI 0.81-1.13).

Conclusions: ARNI use in patients with heart failure is associated with a lower risk of kidney function decline and a similar risk of hyperkalemia compared to ACEIs or ARBs.
Hydralazine-Isosorbide Dinitrate Associated with Reduced All-Cause and Cardiovascular Mortality in Patients on Dialysis with Heart Failure

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Background: Heart failure (HF) is an important contributor to the increased cardiovascular (CV) mortality incidence in ESKD. Therapies targeting HF’s unique pathophysiology in ESKD are lacking. Hydralazine-isosorbide dinitrate (H-ISDN) targets reduced nitric oxide bioavailability and could improve CV mortality in ESKD.

Methods: Adult patients with HF on maintenance dialysis between January 2011 and December 31, 2016 were identified using the United States Renal Data System. There were 6306 patients with at least one prescription for H-ISDN and 75,851 non-users. The primary outcome was death from any cause. Secondary outcomes included cardiovascular death and sudden death. Treatment effects were estimated using stabilized inverse probability weights in Cox proportional hazards regression. Because H-ISDN has been shown to improve outcomes in Black HF patients, we investigated effect modification by race.

Results: Age was similar in H-ISDN users (66 ± 13 years) and non-users (69 ± 13 years) with 50% and 51% men, respectively. H-ISDN (51%) users were more likely to be of Black race than non-users (27%). Dialysis vintage was longer in H-ISDN (25 months) vs non-users (15 months). All characteristics were well balanced in weighted models. Risks of all-cause mortality, cardiovascular death, and sudden death were significantly reduced in H-ISDN users compared to non-users (Table). We did not identify significant effect modification by race.

Conclusions: To our knowledge, this is the first analysis of the impact of H-ISDN on mortality in ESKD. Our results suggest that combination H-ISDN improves survival in dialysis patients with HF.

Long-Term Outcomes After Renal Revascularization for Atherosclerotic Renovascular Disease in the ASTRAL Trial

Philip A. Kalra,1,2 Darren Green,1,2 Natalie Ives.1 The ASTRAL trial investigators Salford Royal Hospital, Salford, United Kingdom; 2The University of Manchester, Manchester, United Kingdom; 3University of Birmingham, Birmingham, United Kingdom.

Background: The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with atherothrombotic renal artery stenosis (RAS) between 2000-2007, randomised 1:1 to medical therapy with or without renal artery stenting. The initial results were presented in 2009 at median follow-up 34.6 months when no benefit of revascularization to renal functional outcomes or cardiovascular events (CVE) were evident. Surviving patients remained under follow up until 2014.

Methods: All available data were analysed to assess whether there was a later impact of revascularization on renal function, CVE and survival, including a composite outcome of renal and CVE outcomes and death (as used in the CORAL trial). Pre-specified sub-group analyses of different categories of renal function, renal length, prior rapid deterioration in kidney function, and severity of RAS. Further post-hoc analysis of patients with severe RAS (defined as bilateral 70% or > 70% RAS in a solitary kidney – global renal ischemia), those with/without proteinuria and a per protocol analysis were performed.

Results: The mean age of the entry population was 70.5 years, mean eGFR 40 ml/min/1.73m², with mean RAS 76% and blood pressure 150/76 mmHg; 83% of the revascularization group underwent attempted stenting. Median follow-up was 56.4 months with 108 patients lost to follow up or withdrawn; 50% of the evaluable population had died, 14% had received RRT and 40% had suffered a 1° CVE. No benefit of revascularization was observed for any outcome in the intention to treat and per protocol analyses, either in the whole population or the pre-specified sub-groups. In the severe RAS sub-group (163 patients) revascularization was associated with a hazard ratio (HR) of 0.74 (0.54-1.01; p=0.062) for the composite renal and CVE outcome and an HR of 0.70 (0.49-1.0) for death (p=0.051).

Conclusions: The long-term follow-up of the ASTRAL trial population showed no overall benefit of renal revascularization to renal and CVE outcomes. It has been highlighted that a proportion of the population had lower risk mild-moderate RAS. The long-term outcomes in patients with severe RAS (global renal ischemia) point to a potential benefit of stenting that may be worthy of further study in a more selected population.

Revascularization in Atherosclerotic Bilateral Renal Artery Stenosis

Sana J. Shaikh, Bilal Al-Khalil, Ling Chen, Anitha Vijayan. Washington University in St Louis, St Louis, MO.

Background: Patients with B/L RAS, if found to have worsening renal failure, refractory HTN or recurrent CHF, are often referred for revascularization despite limited evidence. We hypothesized that revascularization plus medical management prevents adverse outcomes in patients with B/L RAS.

Methods: This was a retrospective single-center cohort study in patients with B/L RAS, B/L RAS in a solitary kidney, U/L RAS with an atrophic or >1cm smaller contralateral kidney or, RAS in a U/L functioning kidney. We excluded patients with non-atherothrombotic RAS, renal artery dissection, atheroembolism and renal transplantation. The primary outcome was Major Adverse Kidney Events (MAKE) at 3 mo. Secondary outcomes were renal events, changes in BP, hospital admissions and all-cause mortality at 1 yr. We used the Chi-square test for the primary outcome and the Chi-square test or two-sample t-tests for the secondary outcomes.

Results: 153 patients were included in the study. There were no differences in the baseline characteristics of the intervention and control groups, except for higher number of smokers in the control cohort (Table 1). There was no difference in MAKE between the 2 groups at 3 mo. At 1 yr, there were fewer admissions for CHF in the intervention group (Table 2). There were no other major differences in secondary outcome measures.

Conclusions: Revascularization for B/L RAS does not improve renal outcomes, BP control or mortality, but may prevent admissions for CHF.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Group (N=69)</th>
<th>Control Group (N=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>68 (98.6)</td>
<td>81 (96.4)</td>
<td>0.413</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (27.5)</td>
<td>22 (26.2)</td>
<td>0.852</td>
</tr>
<tr>
<td>CKD stage 3 or more</td>
<td>39 (56.5)</td>
<td>42 (50.0)</td>
<td>0.421</td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>11 (15.9)</td>
<td>13 (15.3)</td>
<td>0.937</td>
</tr>
<tr>
<td>ASCVD equivalent disease</td>
<td>34 (49.3)</td>
<td>46 (54.8)</td>
<td>0.499</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>29 (42.0)</td>
<td>43 (50.0)</td>
<td>0.259</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>22 (31.9)</td>
<td>20 (33.3)</td>
<td>0.678</td>
</tr>
<tr>
<td>Obesity</td>
<td>20 (29.0)</td>
<td>23 (25.7)</td>
<td>0.678</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>36 (51.2)</td>
<td>62 (73.8)</td>
<td>0.529</td>
</tr>
<tr>
<td>History of smoking</td>
<td>36 (51.2)</td>
<td>61 (73.5)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO1809
Hypertension in a Young Female: A Common but an Intriguing Anecdote
Batool Butt,1 Sohail Sabit,2 1Foundation University Medical College, Rawalpindi, Pakistan; 2National University of Medical Sciences, Rawalpindi, Pakistan

Introduction: Renal artery stenosis accounts for about 1-10% of the 50 million people worldwide with hypertension. All major trials conducted so far on RAS found no benefit with renal artery stenting. Here we report a case of resistant hypertension in a young female who subsequently found to have bilateral renal artery stenosis and ultimately benefited from unilateral stenting.

Case Description: A 35 yrs female, married, with no comorbidities, presented with 03 months history of intermittent episodes of throbbing headache along with dizziness, without any anti hypertensive medicine. Hepatitis B and C serology were negative) USG abdomen showed right shrunken kidney with no renal artery flows on Doppler ultrasound. She was put on four different groups of anti hypertensives including a beta blocker, a calcium channel blocker, thiazide diuretic and an angiotensin receptor blocker but her blood pressure did not settle. Further investigations revealed raised ESR but other tests including autoimmune screening, proteinuria (>300mg/g) was found in 24,4% (n=10) of the patients. A significant reduction of proteinuria was found in the patients who received RDN (p < 0.05).

Results: Currently there are 641 patients treated with the Symplicity Spyral catheter (baseline office BP 168±25 mmHg, 4.6±1.5 prescribed anti-hypertensive medication classes, mean age 60.5 ± 12.5 years, 56.9% male, 42.5% history of cardiac disease, 37.2% type II diabetes mellitus, and 19.1% renal insufficiency with eGFR < 60 ml/min/1.73m²). At 3 years, there were no cases of new renal artery stenosis >70% or renal artery re-intervention. Rates of other adverse events at 3 years included new onset end stage renal disease (2.4%), cardiovascular death (1.6%) and myocardial infarction (0.8%). Mean change in eGFR from baseline to 3 years was -6.5±15.7 mL/min/1.73m². Changes in mean 24-hour and office BP from baseline to 6, 12, 24, and 36 months per standard of care. Adverse events were collected out to 3 years. In this analysis, we present safety and efficacy data for patients who received RDN with the multi-electrode Symplicity Spyral catheter in GSR.

PO1810
Long-Term Safety and Efficacy of Renal Denervation with the Symplicity Spyral Catheter in the Global SYMPLICITY Registry
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Background: Catheter-based renal denervation (RDN) therapy targets upregulation of the sympathetic nervous system to treat hypertension. Results from recent randomized sham-controlled clinical trials have demonstrated the safety and efficacy of RDN, but long-term safety and durability of the procedure in real-world patients is also important.

Methods: The Global SYMPLICITY Registry (GSR) is a prospective, international registry of patients who receive radiofrequency RDN treatment due to uncontrolled hypertension or conditions associated with excessive sympathetic nervous system activation. Office and ambulatory blood pressure (BP) levels were measured at baseline, 3, 6, 12, 24, and 36 months per standard of care. Adverse events were collected out to 3 years. In this analysis, we present safety and efficacy data for patients who received RDN with the multi-electrode Symplicity Spyral catheter.

Results: Currently there are 641 patients treated with the Symplicity Spyral catheter (baseline office BP 168±25 mmHg, 4.6±1.5 prescribed anti-hypertensive medication classes, mean age 60.5 ± 12.5 years, 56.9% male, 42.5% history of cardiac disease, 37.2% type II diabetes mellitus, and 19.1% renal insufficiency with eGFR < 60 ml/min/1.73m²). At 3 years, there were no cases of new renal artery stenosis >70% or renal artery re-intervention. Rates of other adverse events at 3 years included new onset end stage renal disease (2.4%), cardiovascular death (1.6%) and myocardial infarction (0.8%). Mean change in eGFR from baseline to 3 years was -6.5±15.7 mL/min/1.73m². Changes in mean 24-hour and office BP from baseline to 6, 12, 24, and 36 months are shown in the Figure.

Conclusions: Office and 24-hour BP were significantly reduced from baseline at all follow up time-points after RDN with the Symplicity Spyral catheter, with no instances of renal artery re-intervention.

Funding: Commercial Support - Medtronic

PO1811
Endovascular Renal Denervation Efficacy in a Five-Year Follow-Up
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Background: Endovascular renal denervation (ERD) is a minimally invasive procedure that uses radiofrequency ablation to burn the nerves in the renal arteries. Renal sympathetic nerves can modulate sympathetic activity at the whole body level, playing an important role in essential hypertension. This study aims to evaluate ERD efficacy in the treatment of essential hypertension in a five-year follow-up.

Methods: We conducted a prospective study including 41 patients with essential hypertension. ERD was performed using Simplicity Probe or Spyral. Blood pressure (BP) was evaluated using 24-hour ambulatory BP monitoring. Echocardiography was performed using HDI 5000. Clinical and biochemical variables were explored.

Results: A total of 41 patients were included. Overall, 53.7% (n=22) were females with a mean age of 63.6 ± 7.5 years, BMI 30.8 ± 5.2 Kg/m², 17.1% (n=7) had an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m² and 68.3% (n=29) had diabetes. Proteinuria (>300mg/g) was found in 24.4% (n=10) of the patients. A significant reduction in the number of antihypertensive drugs being taken was found after 5 years' follow-up (p<0.001). Despite this reduction, a significant increase in diastolic blood pressure

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Hypertension and CVD: Clinical, Outcomes, and Trials

POI182

Potential Benefits of Asymptomatic Hyperuricemia Treatment: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Dhir N. Gala,1 Kireillos S. Said,2 Nuala A. El-Shafat,3 Allison Parrill,4 Hadir S. Mohamed,5 Nada Abdellahim,5 Mostafa A. Amin,5 Hassan S. AbdalLaham,5 Majd Alahmar,4 Nguyen Tien Huy,5 Mohammed Abdel Gawad.6 1American University of the Caribbean School of Medicine BV, Curacao, Sint Maarten (Dutch part); 2Alexandria University Faculty of Medicine, Alexandria, Egypt; 3Al-Azhar University Faculty of Medicine, Cairo, Egypt; 4University of Istanbul, Istanbul, Turkey; 5Cairo University Kastr Alainy Faculty of Medicine, Cairo, Egypt; 6Mansoura University Faculty of Medicine, Mansoura, Egypt; 7Gawad Nephrology Clinic, Alexandria, Egypt; 8School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan.

Background: Asymptomatic hyperuricemia is strongly associated with an increased risk for chronic kidney disease and cardiovascular conditions. However, many current guidelines suggest no medical treatment for patients with asymptomatic hyperuricemia. We aim to systematically analyze randomized controlled trials with serum uric acid-lowering medication in the treatment of patients with asymptomatic hyperuricemia.

Methods: A literature review of seven medical databases (Scopus, Clinical Gov, Pubmed, Web of Science, Google Scholar, VHL, and GHL) for randomized controlled trials related to the treatment of asymptomatic hyperuricemia was conducted. Bias was evaluated using the Cochrane Risk of Bias 2 tool. Standard differences of means of variables of interest were combined across studies to compare the effects of uric acid lowering treatment versus control. Using the Comprehensive Meta-analysis program, fixed-effects and random heterogeneity model, forest plots were created for each variable of interest.

Results: Analysis of eleven studies showed significant decreases in creatinine [−0.302 (95% CI: −0.599, −0.005)], systolic blood pressure [−0.277 (95% CI: −0.5, −0.055)], and serum uric acid [−1.972 (95% CI: −2.145, −1.800)] in the treatment versus control group. Furthermore, significant increases in estimated glomerular filtration rate (eGFR) with sensitivity analysis [0.228 (95% CI: 0.027, 0.428)], and high sensitivity-C-reactive protein [0.588 (95% CI: 0.205, 0.971)] were observed in the treatment versus control group. Lastly, non-significant decreases in creatinine clearance in an animal test [−0.113 (95% CI: −0.269, 0.042)], and diastolic blood pressure [−0.312 (95% CI: −0.638, 0.013)] while non-significant increases in hemoglobin A1C [0.394 (95% CI: −0.026, 0.813)] and fasting glucose level [0.117 (95% CI: −0.145, 0.380)] were found in the treatment versus control group.

Conclusions: This study showed that uric acid lowering treatment of patients with asymptomatic hyperuricemia may be beneficial in those with elevated creatinine and blood pressure, and decreased eGFR.

POI183

Urinary Glycogen Synthase Kinase β3 Level Predicts the Progression of Hypertensive Nephrosclerosis

LinFeng Zheng, Cheuk-Chun Szeto. Department of Medicine & Therapeutics and Li Ka Shing Institute of Health Sciences (LiHSI), Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong.

Background: Hypertensive nephrosclerosis (HTN) is a serious consequence of prolonged hypertension. In the United States, HTN is the second most common cause of end-stage kidney disease. Recently, emerging evidence suggests that glycogen synthase kinase (GSK) β3 is a key factor in the progression of diabetic kidney disease (DKD). However, it remains uncertain whether the role of GSKβ3 is specific for DKD or a generic mediator of renal damage irrespective to the underlying cause.

Methods: We performed correlation analysis with the frozen and fixed HTN patients. Their GSKβ3 level in urinary supernatant was measured by conventional ELISA, and GSKβ3 mRNA level in urinary sediment was measured by quantitative polymerase chain reaction. The results were compared to the baseline kidney function and the subsequent risk of renal function deterioration.

Results: The average urinary GSKβ3 level was 212.67±47.74 ng/mL by conventional ELISA, and GSKβ3 mRNA level in urinary sediment (r=0.821, P<0.0001). Urinary GSKβ3 level significantly correlated with baseline glomerular filtration rate (GFR) (r=−0.751, P=0.010) and the slope of GFR decline (r=−0.397, P=0.033). Patients with a high urinary GSKβ3 level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSKβ3 level (P<0.022 and P=0.044, respectively). Similarly, urinary GSKβ3 mrRNA level also significantly correlated with baseline GFR (r=−0.582, P=0.0001) and the slope of GFR decline (r=−0.402, P=0.022). Patients with a high urinary GSKβ3 mrRNA level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSKβ3 mrRNA level (P<0.022 and P=0.044, respectively).

Conclusions: These results demonstrated that urinary GSKβ3 level correlates with the rate of kidney function loss in patients with biopsy-proved HTN, and urinary sediment GSKβ3 mRNA level appears to be a good prognostic marker than urinary GSKβ3 level by ELISA. Our results suggest that GSKβ3 is a generic mediator for the progression of chronic kidney disease and is not specific for DKD.

Funding: Clinical Research Support, Government Support - Non-U.S.

POI184

Deletion of the Dopamine D2 Receptor in the Renal Proximal Tubule Increases Blood Pressure on Low-Salt Diet and Decreases Blood Pressure on High-Salt Diet: A Case of Inverse Salt Sensitivity

Laurenzo D. Asico, Shaun C. Moore, Pedro A. Jose, Ines Armando. The George Washington University School of Medicine and Health Sciences, Washington, DC.

Background: The dopamine D2 receptor (D2R) in the kidney is important in maintaining renal blood pressure (BP) and preventing inflammation and tissue injury. Global D2R gene (Drd2) knockdown or 1 renal-selective D2R downregulation in the mouse increases BP and results in renal inflammation, tubular injury, and fibrosis. To study the D2R deletion in the renal proximal tubule, we generated Dnd2-fl/fl; Pgc1α-Cre mice (D2R−/−) that lack D2R only in the renal proximal tubule and Dnd2-fl/fl; Pgc1α-Cre-Drd2−/− mice that do not have the deletion.

Methods: Mice were genotyped for Dnd2−/− and a smaller amplicon representing the Cre deletion mutant. We studied male mice on normal salt (NS; 0.4% NaCl), high (HS; 1% NaCl), and low (LS; <0.08% NaCl), and low (LS; <0.08% NaCl).

Results: On NS diet, male D2R−/− had slightly higher BP, measured under anesthesia, than male D2R−/− mice (106±1 vs 101±2 mmHg, n=15/group; P<0.05). On HS diet D2R−/− mice had lower BP than D2R+/+ mice (100±3 vs 107±2 mmHg; P=0.04; n=12) but on LS diet D2R−/− had higher BP than D2R+/+ mice (125±5 vs 103±4 mmHg; P=0.01; n=7). Both the decrease in BP on HS diet and the increase in BP on LS diet, relative to BP on NS diet, were confirmed by telemetry in conscious mice. These data indicated that D2R deletion only in the renal proximal tubule impairs the normal responses to changes in salt intake. On the diet the renal mRNA mrRNA expression of Na/K ATPase, NCC, and D2R were similar in both groups. On HS diet NHE3 and NCC mrRNA were lower in D2R−/− than D2R+/+ mice (NHE3: 0.7±0.02 vs 1.0±0.03 fold-change; P<0.05; n=4-5/group; NCC: 0.5±0.01 vs 1.0±0.09 fold-change; P<0.05) while Na/K ATPase was similar in both groups. On LS diet NHE3, Na/K ATPase, and NCC expression were higher (P<0.05) in D2R−/− than in D2R+/+ mice.

Conclusions: There are marked differences in the response to changes in dietary salt intake on BP and renal expression of sodium exchanger/transporter/pump in mice lacking D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis.

Funding: Other NIH Support - NIH R01 grants.

POI185

Renal Proximal Tubule-Specific Expression of the NKA/Src Receptor Complex in the Mouse: Evidence for Sexual Dimorphism


Background: The Na+/K’-ATPase (NKA) expressed on the basolateral membrane of renal proximal tubule (RPT) cells serves an anti-natriuretic enzymatic function through its classically recognized ion-pumping properties. There is also pharmacological evidence that, through a Src-mediated mechanism, Na/K-ATPase α1 serves a counteracting natriuretic receptor function that reduces NKA- and NHE3-mediated transport, leading to decreased transepithelial Na+ flux. No studies have been performed to confirm the role of NKA/Src signaling in renal proximal tubule (RPT) cell signaling.

Methods: To test this genetically, we generated RPT cells and mice lacking D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis.

Results: In male mice, expression of NKA/Src receptor complexes is significantly lower in females by 62% (n=6-8, P<0.05, n=2-3/group). In contrast, the NKA/Src receptor complexes are significantly higher in females by 42% (n=6-8, P<0.05, n=2-3/group). The NKA/Src receptor complexes were significantly higher in females by 42% (n=6-8, P<0.05, n=2-3/group).

Conclusions: There are marked sex differences in the expression of NKA/Src receptor complexes in the RPT. These results may have important implications for renal proximal tubule physiology. The presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. However, the presence of D2R variants, D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis.

Funding: Other NIH Support - NIH R01 grants.
**PO1816**

Sex-Dependent Regulation of the WNK-NCC Pathway via Ubiquitination in Response to Dietary High Salt Intake in Young Sprague-Dawley Rats

Kyoung Kim, Mohammed Z. Ferdaus, Richard D. Wainford. Boston University School of Medicine, Boston, MA.

**Background:** The thiazide-sensitive Na\(^+\)-Cl\(^-\) cotransporter (NCC), located in the apical membrane of distal convoluted tubule, fine-tunes sodium reabsorption and regulates blood pressure. The NCC is downregulated by high salt intake in normotensive salt resistant rats. These studies investigated the potential mechanistic pathways by which NCC is degraded in response to high salt intake in male and female Sprague-Dawley (SD) rats.

**Methods:** 3-month-old normotensive male and female SD rats were fed a normal salt (NS; 0.6% NaCl) or HS (4% NaCl) diet for 21 days. On day 21, the kidneys were collected and ~200 mg of the renal cortex was used to measure the expression of total NCC, WNK1, WNK4, Nedd4-2, Sortilin, KLHL3, and calcineurin using immunoblotting (N=5–6/group).

**Results:** A 21-day HS diet evokes the suppression of total NCC protein expression in young normotensive male and female SD rats. A HS diet downregulated WNK1 in male but not female SD rats. A HS diet suppresses the expression of the full-length and short WNK4 variants in female SD rats only. There was a trend for HS to increase Nedd4-2 expression in male SD rats (P=0.06), in contrast female rats downregulated Nedd4-2 in response to HS. The expression of sortilin, KLHL3, and calcineurin was suppressed by a HS diet in female rats only.

**Conclusions:** These data suggest that response to a HS diet young female SD rats exhibit greater ubiquitin-dependent proteolytic and lysosomal degradation of the NCC than young male SD rats to regulate sodium homeostasis and blood pressure via a WNK-dependent signaling pathway.

**Table 1**: NS, 0.6% NaCl; HS, 4% NaCl. *P<0.05 vs. respective NS Group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male</th>
<th>Female</th>
<th>NS</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCC expression (full length)</td>
<td>1.00±0.01</td>
<td>1.00±0.09</td>
<td>0.93±0.05*</td>
<td></td>
</tr>
<tr>
<td>NCC expression (short form)</td>
<td>1.50±0.32</td>
<td>0.93±0.03</td>
<td>0.47±0.06*</td>
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</tr>
<tr>
<td>NCC expression (Nedd4-2)</td>
<td>1.00±0.01</td>
<td>1.00±0.09</td>
<td>0.93±0.05*</td>
<td></td>
</tr>
<tr>
<td>NCC expression (Sortilin)</td>
<td>1.00±0.01</td>
<td>0.97±0.05</td>
<td>0.67±0.10*</td>
<td></td>
</tr>
</tbody>
</table>

**PO1818**

Empagliflozin Prevents Impaired Sensitivity of Afferent Neurons with Renal Axons During a High-Salt Diet

Kristina Rodionova,1 Tilmann Ditting,1,2 Laura Woppeer,1 Karl F. Hilgers,1 Peter Linz,1 Nada Cordasic,1 Christian Ott,1 Mario Schiffer,1 Roland E. Schneider,1 Kerstin U. Amann,1 Roland Veelken,1,2 1Universitätsklinikum Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; 2Paracelsus Medizinische Privatuniversität - Nuremberg, Erlangen, Germany; 1Universitätsklinikum Erlangen, Abteilung für Nephropathologie, Erlangen, Germany.

**Background:** Afferent renal nerve pathways likely play a role in salt sensitive hypertension. We recently reported that high salt diet (HS) impairs these afferent renal pathways in rats. Now we tested the hypothesis that during HS a decrease in sensitivity of renal afferent neurons is prevented by the SGLT2 inhibitor empagliflozin.

**Methods:** Respectively of groups of rats were put on HS containing 8% NaCl or a normal diet. Two groups (HS, controls) received empagiflozin 20 mg/kg BW/day orally. Renal denervation (DNX) was performed retrogradely labeled with DiI. In culture, isolated dorsal root ganglion neurons (DRG Th1-L2) with HS afferent renal afferent axons were investigated electrophysiologically using current clamp mode to assess action potential generation during current injection (neurons were characterized as tonic highly active (>5 action potentials, AP) and phasic less active neurons (≤5 AP upon stimulation).

**Results:** In neurons from rats on HS, the relation of tonic highly active neurons to less active phasic neurons shifted consistently towards phasic units (63.8% tonic neurons in controls vs. 42%* on HS, *P<0.05, t-test). However, continuous treatment with empagliflozin preserved the proportion of tonic neurons as in controls (67.9% on HS with concomitant administration of empagliflozin). In controls, empagliflozin did not affect the proportion of tonic to phasic neurons (63.8% tonic neurons in controls vs. 67.9% on HS & empagliflozin, p=0.7, t-test). Blood pressure and heart rate were not altered by HS and/or treatment with any chosen dose of empagliflozin.

**Conclusions:** These data suggest that response to a HS diet young female SD rats exhibit greater ubiquitin-dependent proteolytic and lysosomal degradation of the NCC than young male SD rats to regulate sodium homeostasis and blood pressure via a WNK-dependent signaling pathway.

**PO1819**

The Role of Histaminergic System Components in Renal Function During Salt-Sensitive Hypertension

Federico Spires,1,2 Mark D. Ditting,1,2 Ryan Schibalski,1,2 Samantha M. Perez,2 Mikhail Fomin,1,2 Morgan J. Spicer,1,2 Sergey N. Arkhipov,2 Callie A. Clarke,2 Thelma Amnoch,2 Tengis S. Pavlov,2 Daria Ilatovskaya,1,2 1Augusta University, Augusta, GA; 2Medical University of South Carolina, Charleston, SC; 3Henry Ford Health System, Detroit, MI.

**Background:** Up to 50% of hypertensive patients have salt-sensitivity (SS), a condition characterized with an increase in blood pressure in response to salt intake. The abnormal activation of the immune response is a major contributor to SS hypertension and renal injury. Histamine and its receptors (HRs) are a complex system of immunoregulators that have been linked to renal disease development. It is known that the Dahl SS rat fed a high salt diet develops hypertension accompanied with elevated levels of inflammatory factors. Methods: Male Dahl SS rats at 8 weeks of age were placed on either a 0.4% (normal salt; NS, control) or 4% (high salt; HS, hypertensive group) NaCl diet for 21 days to induce SS hypertension. An additional group of animals received 3 injections of ranitidine (RAN; HR2 blocker, 25 mg/kg) or saline (VEH, 2.5 ml/kg) pre- and post- the HS challenge to test the effects of HR2 blockage on renal function.

**Results:** Using immunohistochemistry, we established the expression of all four HRs as well as histamine-metabolizing and catabolizing enzymes, along with the nephrin with a pronounced expression in the glomerulus, proximal tubule and the distal tubules. Interestingly, we observed a decrease in histidine decarboxylase, and an increase in histamine N-methyltransferase in the kidney of HS diet fed rats, suggesting a shift in renal histaminergic tone. RAN treatment pre-HS resulted in a significant decrease in renal volume (1.89 ± 0.20 vs. 1.60 ± 0.18 ml/100g, p=0.012, in VEH vs RAN groups respectively) and water consumption (14.3 ± 2.25 vs. 11.9 ± 1.69 ml), along with elevated C1 excretion (728.4 ± 287.4 µM vs 1107.8 ± 416.6 µM). Post-HS RAN treatment yielded a significant increase in urine osmolality (1313.2 ± 319.7 vs 1659.5 ± 359.2 mOsm).

**Conclusions:** These data suggest that response to a HS diet young female SD rats exhibit greater ubiquitin-dependent proteolytic and lysosomal degradation of the NCC than young male SD rats to regulate sodium homeostasis and blood pressure via a WNK-dependent signaling pathway.

**Table 1**: NS, 0.6% NaCl; HS, 4% NaCl. *P<0.05 vs. respective NS Group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male</th>
<th>Female</th>
<th>NS</th>
<th>HS</th>
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<td>NCC expression (full length)</td>
<td>1.00±0.01</td>
<td>1.00±0.09</td>
<td>0.93±0.05*</td>
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PO1820
Salt-Induced Blood Pressure Elevation in Females Is Associated with Increased Arachidonic Acid Metabolites
Jeanne A. Ishimwe, Annet Kirabo, Fernando Eliovich, Jane F. Ferguson. Vanderbilt University Medical Center, Nashville, TN.

Background: Excess dietary sodium (Na+) intake is a major risk for salt-sensitive hypertension and cardiovascular disease. Several clinical trials have found that women are more salt-sensitive than men, but the contributing sex-specific mechanisms are poorly understood. Arachidonic acid (AA) and its metabolites play a role in the pathophysiology of hypertension. We hypothesized that women have greater blood pressure (BP) elevation in response to Na+ intake that is associated with higher AA metabolites than men.

Methods: Plasma AA metabolites were measured via a metabolomics analysis in volunteers who completed a validated 3-day food record to estimate dietary Na+ intake before the study visit where BP was measured. Based on the recommendations by the American Heart Association, we classified daily Na+ intake <2.3 g as normal salt, and high salt for subjects consuming a 2.3 g Na+. Spearman correlation was used to assess the relationship between Na+ intake and AA metabolites.

Results: Women (n=81) displayed a stronger relationship between BP and Na+ intake than men (n=49) (r=0.372; p=0.001 vs. r=0.317; p=0.026). The relationship between Na+ intake and BP was stronger in white (n=46, r=0.417; p=0.004) than in black (n=22, r=0.338; p=0.012) women and conversely stronger in black (n=27, r=0.380; p=0.034) than white (n=32, r=0.251; p=0.166) men. We measured plasma levels of palmitate and linoleate, both upstream of AA synthesis, AA, and 12-Hydroxyeicosatetraenoic acid (12-HETE) an AA metabolite. In subjects consuming a high Na+ diet (women 28, men 25) levels of linoleate (1.211 ± 0.330 vs. 0.869 ± 0.170; p<0.001), palmitate (1.155 ± 0.292 vs. 0.924 ± 0.233; p= 0.003), AA (1.119 ± 0.242 vs. 0.965 ± 0.201; p=0.015) and 12-HETE (1.329 ± 0.925 vs. 0.902 ± 0.526; p=0.0469) were higher in women. In contrast, no sex differences in any of these parameters were observed between men and women consuming a normal salt diet.

Conclusions: Our findings suggest that AA and its metabolites may account for sex and perhaps also racial differences in salt sensitivity of BP. Further study of AA and its metabolites may shed light on the mechanisms of the sex differences in salt sensitivity.

Funding: Other NIH Support - NHLBI

PO1821
Gstm1 Genotype Affects Metabolic Response in Hypertension
Yves T. Wang, Nhu Nguyen, Thu H. Le. University of Rochester Medical Center, Rochester, NY.

Background: Glutathione S-transferases (GSTs) are a family of enzymes that detoxify electrophiles, including products of oxidative stress. In humans, GST μ-1 (GSTM1) has a common null allele variant, GSTM1/-, which has been linked to elevated oxidative stress in pathophysiological conditions and increased risk and/or accelerated progression of a variety of diseases. Recently, we reported that Gstm1 knockout (KO) mice had increased oxidative stress and augmented kidney injury in angiotensin II (Ang II)-induced hypertension (HTN).

Methods: Kidney tissue was obtained from 12-20 week old male wild-type (WT) and Gstm1 knockout (KO) mice at either baseline (no treatment) or following 4 weeks of Ang II-induced HTN via mini-osmotic pump at 1000 ng/kg/min. For each animal, a kidney was excised and snap frozen. For qPCR, mRNA was extracted from an homogenized kidney and used to create cDNA, followed by probing for a panel of 18 GSt genes. For metabolomics, frozen tissue was ground to a fine powder and sent to Metabolon (Morrisville, NC) to obtain a global metabolic profile.

Results: Analysis of qPCR results showed no significant alterations in the expression of GSt genes between WT and KO mice, except for the expected loss of Gstm1 in KO mice. Metabolomics analysis yielded data for 926 metabolites, with expected significant differences due to Ang II treatment particularly in inflammatory and oxidative stress pathways. Ang II treatment also increased inflammatory and oxidative stress-related effects and further increased 131 (14%) significantly changed interactions between genotype and treatment. Comparing Ang II-treated KO and WT mice, there was a significant increase in metabolite abundance in the membrane and glutathione pathways, including the transulfuration pathway linking them. Furthermore, there was an increase in carnitine and asarone and a decrease in several lipid peroxidation markers.

Conclusions: The loss of GSTM1 in Ang II-induced HTN did not elicit a significant compensatory upregulation of mRNA of other GSTs. It is likely other antioxidant pathways are upregulated based on the altered metabolite abundances. However, based on previous results in treated KO mice, any compensatory mechanism is insufficient to protect against the oxidative stress-induced kidney damage. Further research should be pursued to elucidate the oxidative stress-related specific substrates of GSTM1 that are not detected by other pathways.

Funding: NIDDK Support

PO1822
HMGB-1 Activates Mineralocorticoid Receptor-Dependent Endothelial Cell Injury via Receptor for Advanced Glycation End Products
Tomoyuki Otuka,1 Seiji Ueda,1 Hajime Nagasawa,1 Teruyuki Okuma,1 Koji Satô,1 Takanori Matsui,2 Sho-ichi Yamagishi,3 Yusuke Suzuki,1* Juntendo University Faculty of Medicine, Bunkyo-ku, Japan; 2Showa University Faculty of Medicine, Shinjuku-ku, Tokyo, Japan; 3Kurume University Faculty of Medicine, Kurume-shi, Japan.

Background: Endothelial dysfunction plays a central role in the pathogenesis of cardio-renal syndrome. High mobility group box-1 (HMGB-1) is a protein with various roles in different cellular compartments, and indirectly regulates the activity of transcription and DNA repair in the nucleus. On the other hand, during tissue damage, it is released into the extracellular environment as damage-associated molecular patterns (DAMPS). HMGB-1 is reported to be elevated in EKD patients and be involved in endothelial dysfunction through binding to toll like receptor (TLR) and receptor for advanced glycation end products (RAGE). In addition, we recently demonstrated that RAGE-mediated Rac1 activated mineralocorticoid receptor (MR) and resulted in podocyte damage. In the present study, we hypothesized that crosstalk between HMGB-1/ RAGE and Rac1-MR pathways could contribute to endothelial dysfunction in kidney diseases.

Methods: In the present study, we investigated whether HMGB-1 could activate Rac1-MR axis and induce endothelial injury in cultured endothelial cells (HUVECs) by assessing expression levels of genes for MCP-1 and cell adhesion factors (ICAM-1, VCAM-1) with or without administration of RAGE aptamer or MR blocker (esaxerenone, 1μM).

Results: HMGB-1 supplementation significantly increased GTP-bound Rac1 and enhanced MR translocation into the nucleus in HUVECs. We also found that RAGE expression was enhanced by HMGB-1 and RAGE aptamer completely abolished Rac1 activation and MR translocation observed in HMGB-1 exposed HUVECs. HMGB-1 also upregulated MCP-1, ICAM-1, and VCAM-1 in HUVECs, all of which were significantly blocked by pretreatment of RAGE aptamer as well as MR blocker.

Conclusions: These results suggest that there may be a close relationship between HMGB-1/ RAGE axis and Rac1/ MR activation, thus contributing endothelial injury. Using RAGE aptamer or MR blocker could be novel therapeutic strategies against endothelial dysfunction in patients with kidney diseases.

Funding: Other NIH Support - NHLBI R35 HL135749 to A.S., Veterans Affairs Support, Private Foundation Support
**Effect of Tochu Extract and Its Component Geniposidic Acid on Renal Hemodynamics and Hypertensive Renal Damage**

**Akihiro Tojo, Hiroshi Satonaka, Toshihiko Ishimitsu. Dokkyo Medical University, Mibu, Japan.**

**Background:** Aqueous extract of Eucommia ulmoides (Tochu) leaf is used as Tochu tea in Japan and has the effect of lowering blood pressure. We investigated the effects of Tochu extract and its component geniposidic acid on renal hemodynamics and hypertensive renal damage in Dahl salt-sensitive hypertensive rats (DS).

**Methods:** DS rats received 1% saline solution from 4 weeks of age. After the blood pressure reached 150 mmHg or higher at 9 weeks of age, the rats were treated with 1% saline solution (DSHS), or 1% saline added 0.5% Tochu extract (DSHS + T) or, 1% saline added 0.2% geniposidic acid (DSHS + G) for another 4 weeks. DS rats fed with tap water were used as controls (DSLS). At 13 weeks, renal plasma flow (RPF) was measured by renal clearance study, and immunostaining and PCR of NADPH oxidase, eNOS, sodium transporters and fibrinotic factors were performed.

**Results:** Blood pressure was significantly increased in DSLS rats compared to DSHS rats (196 vs.144 mmHg, p<0.01), which was significantly decreased in DSHS + T rats (158 mmHg) and DSHS + G rats (162 mmHg). Vascular resistance of afferent arterioles was significantly increased in DSHS rats compared to DSLS rats, and was decreased in both DSHS + T and DSHS + G rats. RPF was significantly higher in DSLS rats than in DSHS rats associated with decreased renal vascular resistance (p <0.05). In DSHS rats, NADPH oxidase expression and superoxide production were increased, with increased TGF-beta, procollagen 1, fibronectin and renal fibrosis. These were suppressed in DSHS + T and DSHS + G rats. NO production by eNOS was decreased in DSHS rats, but the treatment groups increased eNOS expression and NO production in the vascular endothelium, resulting in decreased renal vascular resistance and improved renal blood flow. Urinary sodium excretion was significantly higher in DSLS rats than in DSHS rats with decreased sodium chloride co-transporter (NCC). However, there was no further change in NCC or other sodium transporters in the treatment groups, and the high urinary Na excretion in the treatment groups was due to the increased RPF.

**Conclusions:** Tochu and geniposidic acid suppressed NADPH oxidase and increased eNOS in DS rats, resulting in improved blood pressure, renal hemodynamics and renal damage.

**Funding:** Commercial Support - Kobayashi Pharmaceutical Inc., Osaka, Japan

**Effect of Uremia on Endothelial Cell Damage Is Mediated by Excessive Neutrophil Extracellular Trap Formation**

**Jwa-kyung Kim, Hoi Woul Lee, Sung gun Kim. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.**

**Background:** Uremia is a clinical syndrome characterized by accumulation of various uremic toxins and associated metabolic abnormalities in chronic kidney disease (CKD). Patients with CKD are at increased risk for cardiovascular (CV) disease and death, and endothelial dysfunction may be a key uremia-specific risk factor. However, the mechanism by which uremia influences endothelial dysfunction is still unclear. We report a role for excessive neutrophil extracellular trap (NET) formation induced by uremic serum on endothelial cell (EC) injury.

**Methods:** Plasma nucleosome and myeloperoxidase-DNA, representative markers of in vivo NETs, and the intracellular adhesion molecule (ICAM)-1 level were measured in incident hemodialysis (HD) patients and healthy volunteer (HV), and their prognostic role was evaluated. For in vitro study, we differentiated HL-60 cells into neutrophil-like cells (dHL-60) by applying retinoic acid, and the effect of uremic serum on dHL-60 and endothelial cells determined.

**Results:** The amount of in vivo NETs were significantly higher in incident HD patients compared to HV, and the markers were strongly associated with ICAM-1 levels. In particular, nucleosome and ICAM-1 levels were independent predictors of a composite endpoint, all-cause mortality or vascular access failure. In vitro, uremic serum derived from HD patients showed significantly increased NETs formation from dHL-60, and these NETs significantly decreased EC viability and induced apoptosis. In addition, the ICAM-1 level in HUVEC supernatant was significantly increased by uremic serum-induced NETs compared to control serum-induced NETs.

**Conclusions:** Dysregulated neutrophil activities in the uremic milieu may play a key role in endothelial damage and vascular inflammatory responses.

**Contributions of Obesity and Hypertension to Progression of Cardiorenal Syndrome in Non-Diabetic Obese Female ZSF1 Rats**

**Isabel T. Nguyen, Jaap A. Joles, Mariianne C. Verhaar. Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, Netherlands.**

**Background:** Obesity and hypertension are highly prevalent in patients with cardiorenal syndrome (CRS). Insight into how these comorbidities individually contribute to disease progression is required to improve treatment strategy. We dissected the separate contribution of obesity and worsening hypertension by deoxycorticosterone acetate (DOCA) plus high salt diet in the obese female ZSF1 rat, a model of metabolic CRS in the absence of diabetes [Nguyen, PLoS One 2020]. We hypothesize that in obese non-diabetic female ZSF1 rats obesity has a profound effect on functional progression of CRS while hypertension mainly affects fibrosis and inflammation.

**Methods:** Systolic blood pressure (SBP), renal and cardiac function were assessed biweekly in lean and obese female ZSF1 rats from 12 to 26 weeks of age. From 19 weeks, rats were implanted with either a DOCA pellet and fed a high salt (6% w/w) diet or with a placebo pellet and fed a normal salt diet. At 26 weeks of age, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed under isoflurane anesthesia. Subsequently, rats were sacrificed and tissues processed for analysis of renal and cardiac damage and inflammation.

**Results:** Obese versus lean placebo rats showed elevated E/e' ratio from 12 weeks, indicative of diastolic dysfunction. From 24 weeks obese compared to lean placebo rats developed proteinuria with lower GFR at 26 weeks of age. DOCA-salt markedly increased SBP in obese but not lean rats, despite similarly high natriuresis compared to placebo rats. ERPF was increased by DOCA-salt in lean but not obese rats. DOCA-salt worsened proteinuria and glomerulosclerosis in obese rats. Cardiac fibrosis and glomerular hypertrophy, present in obese rats, were not aggravated by DOCA-salt. However, DOCA-salt increased the number of macrophages in heart, but not in glomeruli of obese ZSF1 rats.

**Conclusions:** Obesity leads to renal and cardiac dysfunction and damage in female ZSF1 rats. Even without worsening of hypertension (DOCA-salt), cardiac dysfunction preceded proteinuria, suggestive of CRS type 2. Our findings suggest that antihypertensive and antiproteinuric treatment at a later stage without initially addressing metabolic risk, even in the absence of diabetes, will not provide adequate functional protection in CRS type 2.

**Funding:** Private Foundation Support

**Association Between Kidney Function and Lipid Levels in Older Adults**

**Shreya Srivastava,1 Josef Coresh,2,3 Casey Rebholz,1 Morgan Grams,1,2 Kunihiro Matsushita,2,3 Seth S. Martin,2 Jung-Im Shin,1 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; ‘Johns Hopkins Medicine, Baltimore, MD.**

**Background:** The associations between kidney function and lipid levels in older adults have not been well characterized. Moreover, it is unknown whether residual atherosclerotic cardiovascular disease (ASCVD) risk after statin use differs by lipid levels other than total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), such as triglyceride (TG).

**Conclusions:** Dysregulated neutrophil activities in the uremic milieu may play a key role in endothelial damage and vascular inflammatory responses.

**Association Between Kidney Function and Lipid Levels in Older Adults**

**Shreya Srivastava,1 Josef Coresh,2,3 Casey Rebholz,1 Morgan Grams,1,2 Kunihiro Matsushita,2,3 Seth S. Martin,2 Jung-Im Shin,1 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; ‘Johns Hopkins Medicine, Baltimore, MD.**

**Background:** The associations between kidney function and lipid levels in older adults have not been well characterized. Moreover, it is unknown whether residual atherosclerotic cardiovascular disease (ASCVD) risk after statin use differs by lipid levels other than total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), such as triglyceride (TG).
Methods: We conducted a cross-sectional study of older adults (≥65 years) using visit 5 data (2011-2013) of the Atherosclerosis Risk in Communities study. Multivariable linear and logistic regression was used to examine the eGFR-lipid associations, stratified by statin use. Among statin users without ASCVD who had LDL-C levels <100 mg/dL, we predicted 10-year ASCVD risk after statin use by TG levels (<150 mg/dL vs. ≥150 mg/dL) across eGFR categories.

Results: The mean age of the study population (n=4965) was 75 (SD 5) years, 58% were female, and 22% were Black. The mean eGFR was 63 (SD 18) ml/min/1.73 m² and 52% were on a statin. In both statin users and non-users, there were no associations between eGFR and total TG or LDL-C. Low eGFR was associated with low high-density lipoprotein cholesterol (HDL-C) and high TG (Figure). Among statin non-users, eGFR <45 (vs. ≥60) was independently associated with low HDL-C (<50 mg/dL) (prevalence=59% vs. 34%, odds ratio=1.86; 95% CI, 1.38-2.51) and high TG (≥150 mg/dL) (31% vs. 20%; 1.31; 1.01-1.70). The results were similar among statin users. Among statin users with LDL-C >100 mg/dL, the prevalence of high predicted ASCVD risk (risk ≥20%) was greater among those with vs. without high TG across all eGFR categories (eGFR ≥60, 66% vs. 59%; 45-59, 78% vs. 73%; eGFR <45, 90% vs. 79%).

Conclusions: We found that low eGFR was associated with low HDL-C and high TG levels, regardless of statin use. Among statin users who achieved adequate LDL-C control, ASCVD risk was still higher among those with high TG compared to those without high TG.

Funding: NIDDK Support

POI1829

Cerebrovascular Dysfunction in CKD

Cortney Steele, Esther Oh, Heather Farmer-Bailey, Rachael L. Reddin, Taylor Struemph, Michel Chonchol, Kristen L. Nowak. University of Colorado-Anschutz Medical Campus, Aurora, CO.

Background: Cerebrovascular dysfunction, characterized by reduced cerebrovascular reactivity, cerebral hypoperfusion, and increased pulsatile flow within the brain precedes the onset of dementia and is linked to cognitive dysfunction. While large-artery vascular dysfunction is prevalent in chronic kidney disease (CKD), cerebrovascular function has not been well characterized to date in moderate-to-severe CKD.

Methods: Using transcranial Doppler, we compared middle cerebral artery (MCA) blood flow-velocity response to hypercapnia (normalized for blood pressure and end tidal CO2) as a measure of cerebrovascular reactivity and MCA pulsatility (a measure of cerebrovascular stiffness) in patients with stage 3-4 CKD vs. age-matched healthy controls using an independent samples t-test. We also administered the trail making test (parts A and B) as an index of processing speed and measured carotid-femoral pulse-wave velocity (CFPWV) as an index of aortic stiffness.

Results: Seven participants with CKD (2F, 68±3 yrs [means±SEM]) had eGFR <60 ml/min/1.73m² (1.31-2.09). MCA pulsatility index was higher (1.08±0.10 vs. 0.85±0.04 A.U.; p=0.05) and normalized MCA blood flow-velocity response to hypercapnia tended to be lower (6.3±4.0 vs. 11.6±7.3 %; p=0.06) in CKD as compared to healthy controls. Trails making part A time was slower (A: 31.8±3.3 vs. 20.2±1.6 sec; p<0.01); part B time tended to be slower (longer time to complete): 71.7±13.6 vs. 42.7±6.2 sec; p=0.07) and CFPVV was higher (1224±115 vs. 811±88 cm/sec; p<0.05) in CKD vs. control. Greater MCA pulsatility index correlated with worse cerebrovascular reactivity (r =-0.63, p=0.01), greater CFPVV (r = 0.65, p<0.01), slower trail making part B time (r =-0.59, p=0.05), and lower eGFR (r = -0.53, p=0.09).

Conclusions: Impaired cerebrovascular function is evident in patients with moderate-to-severe CKD. Increased cerebrovascular stiffness is associated with reduced kidney function, increased aortic stiffness, impaired processing speed, and worse cerebrovascular reactivity.

Funding: Government Support - Non-U.S.

POI1830

Circadian Clock Provides Beneficial Effects Against Endothelial Dysfunction by Regulating Heme Synthesis and Heme Oxygenase 1 Expression

Hidoyuki Negro,1,2 Harvard Medical School, Boston, MA; 2The Graduate School of Project Design, Tokyo, Japan.

Background: The circadian clock is a molecular mechanism that confers 24 hours variations in gene expression and function to regulate number of physiological functions in humans. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. 5-Aminolevulinic acid (ALA) is the common precursor of heme. The iron ion is inserted into P450 to form heme in the mitochondria and incorporated into hemoproteins. Heme is a ligand of REV-ERBα and REV-ERβ which modulate circadian rhythms by binding to the ROR region of CLOK or BMAL1 to suppress the expression of these genes. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of HO-1 expression in the knocked down cells. To synchronize circadian rhythms, serum stimulations were performed. Cells were pre-incubated with or without 1 nM ALA and 0.5 mM sodium ferrous citrate (SFC).

Results: In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression in mice with a dysfunctional circadian rhythm. Bmal1 KO mice display pre-mature aging to have a dramatic proatherogenic phenotype. This phenotype is linked to the regulation of key targets for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. ALA/SFC co-incubation affected the oscillation and phase of core clock genes and led to increase of HO-1. HO-1 levels followed a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherothrombosis by regulating Heme synthesis and HO-1 expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.
**PO1831**

**Bradykinin Reduces Long-Lasting TRPV1-Mediated Inward Currents in Afferent Nonfiring Renal Neurons**

Kristina Rodionova,1 Christina Forray-Strauss,1 Tilmann Ditting,1,2 Karl F. Hilgers,1 Nada Cordasic,3 Peter Linz,3 Christian Ott,3 Roland E. Schmieder,1 Mario Schiffer,1 Kerstin U. Amann,1 Roland Veelken,1

1Universitätsklinik Erlangen Medizinische Klinik 4 Nephrologie und Hypertensiologie, Erlangen, Germany; 2Paracelsus Medizinische Privatuniversität - Nürnberg, Nürnberg, Germany; 3Universitätsklinikum Erlangen, Abteilung für Nephropathologie, Erlangen, Germany.

**Background:** Bradykinin has been reported to be sympathetic excitation via renal afferent nerves. Hence we tested the hypothesis that bradykinin directly stimulates cultivated renal afferent neurons with afferaent axons.

**Methods:** Dorsal root ganglion neurons (TH1-1-2) of rats were investigated in voltage clamp mode to measure inward currents and current clamp mode to assess action potential (AP) generation [neurons classified as tonic (high AP generation upon stimulation), phasic (AP ≤ 5 upon stimulation) or no firing]. Stimulation of TRPV1 receptors by protons (pH 6) with and without the addition of bradykinin (1, 10, 100 µM). 111 DRG renal neurons retrogradely stained with Dil for investigation.

**Results:** Bradykinin (BK) alone did not induce inward current nor APs. Proton stimulation (pH 6) of TRPV1 significantly augmented long-term inward currents (baseline -0.36 ± 0.09 nA vs. -1.39 ± 0.34 nA, p<0.05, mean±SEM) and increased action potential potential in tonic neurons (0 APs/10s vs. 9.57 ± 1.89 APs/10s, p<0.05, mean±SEM). However, the co-stimulation of renal neurons with protons and BK had any effect only in one specific subgroup of renal neurons: it significantly decreased long-lasting currents in non firing neurons (AU stimulation with 100µM BK+pH6: -0.129 ± 0.26 nA, 10µM BK+pH6: -0.0119 ± 0.036 nA, 1µM BK+pH6: -0.063 ± 0.02 nA versus pH 6: -0.312 ± 0.06 nA, *p<0.05*, mean±SEM).

**Conclusions:** Bradykinin was only able to reduce long-lasting, TRPV1 dependent inward currents in non-firing renal neurons. Alterations of inward currents are likely involved in regulating proinflammatory proinflammatory peptides (SP, CGRP). Hence, bradykinin might impair the release of neuropeptides from intrarenal axons of a specific subgroup of renal afferent neurons.

**PO1832**

**The Impact of rs2254524 LSS Polymorphism on Blood Pressure in a New Mouse Model**

Sipontina Paolo,1,2 Citterio Laura,1,3 Menendez-Castro Nada,1,2 U. Cittadenza Elisabetta,1,3 von Manunta Manunta1,2,3 Genomics of Renal Diseases and Hypertension Unit1,2 IRCSS Ospedale San Raffaele, Milan, Italy; 3Università Vita Salute San Raffaele, Milano, Italy.

**Background:** Blood pressure (BP) response to salt intake is associated with hypertension (HTN) and shows great variability among individuals. Endogenous ouabain (EO) is a steroid hormone previously associated with HTN. To dissect EO and HTN link we hypothesized that LSS affects salt-sensitive HTN by regulation of EO biosynthesis.

**Methods:** We generated a knock-in mouse model carrying the rs2254524 SNP variant from LSS CC. The LSS transcript and protein levels were slightly reduced in the Adrenal Gland of LSS AA mice at 3 months of age and in the kidney at 6 months of age. At 3 months of age we observed a faster decline in GFR in hypertensives. We therefore considered two factors: weight loss and typical renovascular lesions. We performed an unbiased analysis of gene expression by RNA-sequencing to identify transcriptional changes in the kidney specific to malignant hypertension (NMH) and compared to non-malignant hypertension (NMH). We considered two factors: weight loss and typical renovascular lesions. This pathway may contribute to the specific kidney injury observed in malignant hypertension.

**Funding:** Government Support - Non-U.S.

**PO1833**

**RNA Sequencing Reveals Induction of Specific Renal Inflammatory Pathways in a Rat Model of Malignant Hypertension**

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**Background:** In malignant hypertension (MH), far more severe kidney injury occurs than in the “benign” form of the disease. The pathogenesis of this peculiar renal injury of malignant hypertension remains incompletely understood. Using a rat model in which some but not all animals develop MH, we performed an unbiased analysis of gene expression by RNA-sequencing to identify transcriptional changes in the kidney specific for malignant hypertension.

**Methods:** Renovascular hypertension in rats was induced by placing a 0.2 mm clip on the left renal artery (2K1C). Five weeks later, all 2K1C rats had developed hypertension. Rats were then sacrificed, and renal cortical RNA was extracted from the right kidney exposed to high blood pressure. To distinguish MH from non-malignant hypertension (NMH), we considered two factors: weight loss and typical renovascular lesions. Differential gene expression was assessed in three groups: MH, NMH and normotensive, sham operated controls (N=5 per group for RNA sequencing, N between 8 and 14 for other analyses).

**Results:** Mean blood pressure measured intraarterially was elevated to a similar degree in MH (207±10 mmHg) and NMH (204±4 mmHg) compared to controls (113±3 mmHg, p<0.05). 886 genes were exclusively regulated in MH only. Principal component analysis revealed a separated clustering of the three groups. The data pointed to an upregulation of many inflammatory mediators in MH including pathways which previously attracted little attention in this setting: Transcripts from all three complement activation pathways were upregulated in MH compared to NMH but not in NMH compared with controls; immunohistochecmistry confirmed conformed deposition in MH but not in NMH.

**Conclusions:** The hypertensive kidney injury in malignant hypertension of 2K1C rats includes a robust expression and deposition of complement components as well as infiltration of neutrophil leukocytes, features which are not observed in the non-malignant course of renovascular hypertension. These pathways may contribute to the specific kidney injury observed in malignant hypertension.

**Funding:** Government Support - Non-U.S.

**PO1834**

**Toll-Like Receptor 4 (TLR4) an Effector of Renal Inflammation and Sodium (Na) Transport**

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**Background:** Na sensitivity of blood pressure (BP) is risk factor for cardiovascular mortality compared to Na resistant subjects. In addition, constrained cholesterol (chole) efflux is novel predictor for future cardiovascular events. Dysregulation of ABCA1, a cholest efflux protein, is implicated in hypertension and kidney disease while ABCA1 ablation in mice augments stimulates TLR4 dependent inflammation. We surmised that tubular ABCA1 depletion similarly enhances TLR4 dependent inflammation in a model of Na sensitivity.

**Methods:** Transgenic mice (GFP/+/GFP+/+), which express CRE in tubular epithelia when fed a low sodium diet, were bred with mice expressing floxed ABCA1 to generate mice deficient in tubular ABCA1 (FF). Western bloting was performed on whole kidney protein lysate, renal plasma membrane (PM), and mpkCCD cells. Amiloride sensitive short-circuit current (Asc) was measured in ureter and static exposed mpkCCD cells.

**Results:** FF mice are phenotypically consistent with Na sensitivity (abstract# 3600350). FF and littermate controls (WT) mice fed a chole enriched diet for 6 weeks, a low Na and a high Na diet for 1 week were euthanized and kidneys extracted. Steady-state protein expression of NRPL3 inflammation increased in ABCA1 deficient (1.5±0.1; n=9) vs WT kidneys (1.0±0.1; P<0.05) or WT kidneys (1.0±0.1; n=9); however, TLR4, a receptor that stimulates NRPL3, was unchanged. Western blolting of renal TLR4 protein showed enhanced TLR4 abundance in FF (1.9±0.3; n=9) vs WT (1.0±0.2; n=3) kidneys. Because Na enriched diets augments urine volume, tubular flow, and, thus fluid shear stress (FSS), the role of TLR4 sensitivity (SR) on renal FSS mediated TLR4 dependent inflammation. We surmised that tubular ABCA1 depletion similarly enhances TLR4 dependent inflammation in a model of Na sensitivity.

**Conclusions:** ABCA1 tubular deficiency enhances TLR4 PM localization and activates TLR4 to induce NRPL3 while a cell model confirms that FSS and reduced TLR4 dependent inflammation.

**Funding:** Veterans Affairs Support, Private Foundation Support
PO1835

T Lymphocytes in Human Hypertension

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Background: Mouse models have shown that T lymphocytes are required for hypertension (HTN) development and accumulate in the vasculature and kidneys. The role of immune cells, including T lymphocytes, remains poorly understood in patients with HTN. Here, we analyzed immune cells in human kidney tissue samples in patients with HTN.

Methods: Human kidney tissue was obtained from the unaffected portions of 631 tumor nephrectomies and included clinical, histological and follow up tissue data. Tissue was microdissected into glomerular and tubular compartments for DNA sequencing. In silico deconvolution of each kidney sample was performed using the CIBERSORTx method to estimate relative cell type fraction and flow cytometry analysis used for validation analyses using cell type specific antibodies in another set of 58 human kidney tissue samples. Regression analyses were used to determine the associations of renal immune cells and clinical parameters. Linear mixed modeling was used to assess longitudinal data.

Results: CD4 and CD8 T-cells were increased in patients with HTN (p=0.05) while T regulatory cells (Tregs) were decreased (0.4% vs. 0.6%, p=0.022). In adjusted models, HTN was associated with older age, Black race, diabetes, decreasing eGFR, and increasing CD4 T-cells (p=0.01). In samples with CKD stages 1-2, older age, lower Tregs and natural killer T-cells and higher CD4 T-cells were associated with HTN, independent of baseline eGFR or the degree of renal fibrosis (p=0.001). In our flow cytometry cohort, HTN was also significantly associated with higher CD4 T-cells, lower Tregs and DCs, but also lower CD8 T-cells, independent of eGFR (p=0.009). Longitudinal data were available for 149 subjects for an average of three years and showed that older age, lower baseline eGFR and higher Th17 cells were associated with lower eGFR over time (p=0.001).

Conclusions: In silico deconvolution resolved a variety of renal immune cells and provided complementary information to flow cytometry analyses in kidney tissue. The multiple T-cell populations were increased in the setting of HTN. Tregs were decreased. These findings were independent of eGFR at CKD stages 1-2. Th17 cell expansion predicted faster eGFR decline. Our results highlight an important association between T-cell populations, HTN, kidney disease and kidney function decline.

Funding: NIDDK Support, Commercial Support - Merck, Boehringer Ingelheim

PO1836

Focal Adhesion Kinase: A Major Regulator of Myocardial Failure in CKD

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Background: The focal adhesion pathway is essential in signal communication between the extracellular matrix and the cytoskeleton. Failure of this signaling pathway results in cytoskeletal dysfunction and has been shown to be intricately involved in the progression of ischemic cardiomyopathy. Whether this occurs in CKD-associated cardiac fibrosis is currently unknown. In this study, our aim was to investigate the role of focal adhesion kinase (FAK), a central component of the focal adhesion pathway in the failing heart in CKD.

Methods: We performed a cross-sectional cohort study of explanted human heart tissues from hemodialysis-dependent (HD, n=19), hypertension with preserved renal function (HTN, n=10), and healthy control (n=21) donors. Left ventricular (LV) tissues were subjected to RNA sequencing, qPCR, and protein analyses. Mechanistic and interference RNA studies using in vitro human ventricular cardiac fibroblast models were also conducted.

Results: Hearts from HD donor exhibited significant myofibrillar disorder (p<0.01) compared to HTN and control. HD and HTN hearts had higher heart weights (p<0.01) and greater LV wall thickness (p=0.01) compared to control hearts. RNA-sequencing revealed that the focal adhesion pathway was one of the most perturbed pathways in HD hearts compared to control. FAK mRNA and protein expression was significantly upregulated (p<0.05), and major cytoskeletal proteins associated with the focal adhesion pathway, including β-actin (p=0.01), β-tubulin (p=0.01), vinculin (p=0.05), and vimentin (p=0.01) were significantly dysregulated in HD hearts compared to controls. Uremic mineral stressors (high phosphate and high calcium) decreased FAK expression as well as β-tubulin (p=0.05) and vimentin, and promoted cleavage of FAK and vimentin, in vitro. Concurrent FAK siRNA transfection and mineral stress significantly decreased both full-length and cleaved FAK expression (p<0.05) and further dysregulated vimentin (p<0.05) and vinculin (p<0.05) expression, in vitro.

Conclusions: FAK and the focal adhesion pathway plays a central role in the development of CKD-associated cardiomyopathy and appears to preserve the dynamic formation of the cytoskeleton in CKD hearts. These findings suggest a potential therapeutic role targeting the focal adhesion pathway in the management of cardiac remodeling in CKD.

PO1837

Dual Action of β2AR-Agonism Confers Protection Against Heart Failure and Renal Dysfunction via Inotropic and Lusitropic Effects and Normalized Cholesterol Homeostasis in a Mouse Model of Alport Syndrome

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Background: Cola3 Alport mice present a model of heart failure with preserved ejection fraction (HFpEF) secondary to CKD. HFpEF is characterized by unresponsive to pharmaceutical intervention. Here, we tested the hypothesis that selective β2AR modulation with salbutamol could alleviate symptoms of CKD and simultaneously augment cardiac function. Secondarily, we investigated the mechanism of actions of such β2AR-mediated therapeutics on cardiac and renal functions.

Methods: Alport mice were injected intraperitoneally with salbutamol or DMSO vehicle as a single bolus of 200 μg/dose in short-term studies or daily with 100 μg/dose for 2 weeks long-term. Cardiac and renal functions, CaMP levels, in vivo renal tubular LDL-C uptake and renal histology were evaluated post-injection.

Results: Short-term, salbutamol improved renal function in parallel with decreased LDLR levels and reduced uptake of LDL-C into renal tubules. Long-term, cardiac diastolic function assessed by isovolumetric relaxation time (IVRT), filling pressures (E/E’), and myocardial performance index, and systolic function reflected by ejection fraction, stroke volume and cardiac output improved significantly in parallel with increased cardiac output. Mechanistically, in the kidney, salbutamol induced IDOL-mediated ubiquitination and subsequent lysosomal degradation of the LDLR via a novel β2AR-mediated, independent pathway involving the Rac1/Cdc42 β1Pix/GEF. β1Pix reversibly sequesters IDOL into a complex with LDLR, thereby blocking the degradation pathway. β2AR stimulation dissipates the complex reactivating IDOL-mediated LDLR degradation thereby re-establishing LDL-C homeostasis and renal function. Using flow cytometry in HEK293T cells, ectopic expression of β1Pix stabilized cell surface LDLR abundance in an IDOL-dependent and PKS1D-independent manner.

Conclusions: β2AR agonism represents a potential treatment strategy to alleviate progression of cardiac and renal failure associated with HFpEF phenogroup 3.

Funding: Other NIH Support - NHLBI, Private Foundation Support

PO1838

Phenotyping CKD-Associated Cardiac Fibrosis

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Background: Myocardial fibrosis is a pervasive and progressive complication in CKD patients. Mechanistically, increased collagen cross-linking has been shown to be critical determinant of tension, stiffness of collagen fibers, and resistance to degradation in ischemic cardiomyopathy, as opposed to increased collagen deposition alone. Whether similar metabolic processes and physiochemical alterations occur in CKD is largely unknown. Herein, we investigated the fibrotic phenotype in CKD-associated cardiomyopathy and the role of disturbed mineral stressors.

Methods: Human left ventricular (LV) tissues were collected from hemodialysis (HD; n=13), hypertensive (HTN; n=8), and healthy control (n=12) donors to compare matrix proteins. Mechanistic in vitro studies involving treatment of human ventricular cardiac fibroblasts (HCFs) with either 1.8-3.8 mM β-glycerophosphate (BGP) or 2.4-5 mM CaCl2 in media were conducted. Protein expression was assessed by immunoblotting.

Results: We report increased trimeric (400 kDa) collagen I (COL1) in LV tissues from HD and HTN (p<0.05) compared to healthy control. Uniquely, mononmeric (150 kDa) COL3 was decreased in HD hearts (p=0.05) compared to HTN and healthy control. Dimerc (250 kDa) or mononmeric COL1 (139 kDa) and other COL3 multimers were not found in any groups. HD and HTN hearts exhibited increased perismin (p<0.05) compared to healthy control. There was no significant difference in fibronectin or α-smooth muscle (αSMA) between groups. We next performed dose-dependent studies in HCFs treated with either BGP or CaCl2. 3.8 mM BGP stimulated increased trimeric but not dimeric COL1 (p=0.05), and reduced mononmeric COL3 (p=0.01) synthesis leading to increased total COL1:3 ratio (p=0.05), in vitro. No other forms of COL1 or COL3 were examined. Additionally, 3.8 mM CaCl2 expression (p=0.01) did not significantly change perismin or α-SMA expression. At 5 mM CaCl2, treatment, this decreased COL3 (p=0.01), fibronectin (p<0.05), and perismin (p<0.05) expression.

Conclusions: Cardiac fibrosis in hearts from HD patients is characterized by increased trimeric COL1 expression and increased COL1:3 ratio that can be driven by disturbed mineral stressors. These changes suggest pathologic cross-linking that can lead to altered mechanical properties and further studies are warranted.

Funding: Other NIH Support - NHLBI, Private Foundation Support

567

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Underline represents presenting author.
PO1839

Plasma Proteins Associated with eGFR and Incident Cardiovascular Events in the Cardiovascular Health Study Cohort

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Background: Proteomics may help identify mechanisms through which low estimated glomerular filtration rate (eGFR) increases risks of heart failure (HF), myocardial infarction (MI), and cardiovascular (CV) death.

Methods: We utilized an aptamer-based assay to measure 1300 proteins among 3185 older adults in the Cardiovascular Health Study. Proteins associated with eGFR were identified using linear regression models. A Bonferroni-corrected p-value less than 7.6x10^-4 was used to account for multiple testing. Proteins significantly associated with eGFR were tested for associations with incident HF, MI, and CV death using Cox-proportional hazard regression adjusting for demographic and clinical variables. We evaluated whether proteins mediated associations between eGFR and incident CV events.

Results: The mean baseline eGFR was 70 ml/min/1.73m^2 and over a follow-up median of 13 years, there were 1033 incident HF, 555 incident MI, and 963 CV death events. 797 proteins were significantly associated with eGFR. Of these, 52, 0, and 22 proteins were associated with incident HF, MI, and CV death, respectively. All proteins associated with HF and CV death significantly mediated the effects between eGFR and incident CHF and CV death, respectively. The 10 proteins most strongly associated with both HF and CV are shown in Table.

Conclusions: eGFR is associated with a large number of plasma proteins. A subset of these proteins are associated with incident HF and CV death and may reflect mechanisms through which reduced eGFR increases the risk of these outcomes.

Funding: Other NIH Support - NHLBI/NIH

PO1841

The Impact of Calcification on Intraplaque Hemorrhage in Coronary Atherosclerosis from Autopsy Samples: The Hisayama Study

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Background: Vascular calcification is the specific feature of arterial change and is often seen in coronary arteries among patients with chronic kidney disease (CKD) and older subjects. The information whether vascular calcification is associated with intraplaque hemorrhage is scarce. We aim to examine how much area of calcification is the highest risk on plaque vulnerability.

Methods: We examined 375 coronary arteries obtained from autopsy samples of subjects with CKD stages 0 to 5 in a general Japanese population. Arteries were divided into quintiles based on vascular calcification area. The association of calcification area with the presence of intraplaque hemorrhage in coronary arteries was estimated by using logistic regression analysis.

Results: Calcification lesions were counted in 149 coronary arteries. All calcification lesions were existed in intima. Subjects in the fourth quintile of calcification area had a significantly higher likelihood of intraplaque hemorrhage than those in the lowest quintile after adjusting for confounders (odds ratio [95% confidence interval], 19.93 [1.48-267.71]), whereas subjects in highest quintile did not (7.86 [0.61-101.70]). The calcification area at highest risk for the presence of intraplaque hemorrhage was 2.02 mm^2, and the risk was constant at greater area than this value in the logistic analysis with restricted cubic spline.

Conclusions: The present study suggests that larger vascular calcification is associated significantly with increased risk for intraplaque hemorrhage, subsequently linking to plaque vulnerability. Above a certain amount of calcification area, these increasing trends may no longer be observed.

PO1842

Radiation Exposure and Coronary Atherosclerosis: Differential Effect of the Radiation Site

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Background: Accelerated coronary artery atherosclerosis is a common complication of thoracic radiation therapy as result of unintended direct cardiac radiation. It is unclear however whether specific areas of the heart are more susceptible to the effects of radiation. In this study we hypothesize that accelerated development of atherosclerotic lesions post radiation (RT) is dependent upon differential sensitivity of specific areas of the heart to the effects of RT.

Methods: Male Apolipoprotein E knockout mice on a high fat diet received 16Gy cardiac RT targeted to the whole or partial (apical or basal) region of the heart at 9 or 16 weeks of age (+5 per group). Atherosclerotic lesions in H&E stained slides and inflammatory infiltrates in the hearts by IHC were assessed 8 weeks following radiation and compared to unirradiated controls.

Results: Our studies show that (1) Subendocardial atherosclerotic lesions at the base of heart in mice irradiated at 9 weeks of age after basal irradiation are comparable to whole heart irradiation. (2) A greater number of atherosclerotic lesions were present in the basal coronary arteries and basal subendocardial vasculature after irradiation of the cardiac base as compared to unirradiated controls in mice irradiated at 16 weeks of age (Table). (3) Apical or whole heart irradiation had no impact on the development of lesions in the basal region of the hearts of 16 week old mice (Table). (4) IL-6 was significantly increased in the serum of mice 6 hours post basal cardiac irradiation (105.10±17.56 pg/ml) when compared to unirradiated controls (29.85a±11.63 pg/ml) demonstrating an early inflammatory response. (5) Infiltration of inflammatory cells (CD45 and CD68) and expression of endothelial adhesion molecules (CD31) were differentially and locally regulated based on the site of irradiation.

Conclusions: Our results indicate that the base of the heart is more prone to development of RT induced atherosclerotic lesions likely due to acute and delayed inflammatory responses. Avoiding this area from direct radiation exposure may improve the quality of life for cancer patients receiving thoracic RT.
Correlations of Creatinine with Biomarkers of Tubular Injury and Secretory Function in Patients Admitted with Heart Failure

PO1843

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Background: Serum creatinine values during hospitalization for decompensated heart failure (ADHF) may not comprehensively capture kidney function. The aim of this pilot study was to evaluate correlations of traditional markers of filtration (serum creatinine) with novel measures of tubular injury and tubular secretion in patients admitted with ADHF.

Methods: Biospecimens were obtained within 24 hours of admission in 61 patients admitted with ADHF at a University of Washington hospital. We measured serum creatinine, urine tubular injury markers (urine NGAL, KIM-1, II-18 and TIMP2 standardized to urine creatinine) and proximal tubular secretory function ([urine concentration]/[plasma concentration] normalized to U,.). We calculated spearman correlations of each kidney measure with each other and admission serum brain natriuretic peptide (BNP).

Results: Serum creatinine poorly correlated to biomarkers of tubular injury (Table 1). Higher serum creatinine was significantly correlated with lower clearance of all secretory biomarkers aside from cinnamoylglycine. Admission BNP did not correlate with serum creatinine or injury biomarkers but had a consistent inverse relationship with secretory biomarkers aside from cinnamoylglycine. Admission BNP.

Conclusions: The results from this pilot study demonstrate that serum creatinine poorly correlates with biomarkers of tubular injury and inversely correlates with tubular secretory clearance in patients admitted for ADHF. More research is needed to understand how filtration, tubular injury, and secretory clearance relate to clinical outcomes and response to treatment in patients with ADHF.

Funding: NIDDK Support

Table 1: Correlation matrix of biomarkers on admission for ADHF

PO1844

RAAS vs. COVID: Case of an 18-Year-Old with New-Onset Hypertension

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Introduction: It has been increasingly known that SARS-CoV-2 causes an imbalance in the Renin-Angiotensin-Aldosterone System (RAAS). Here we present an interesting case of a young man, who presented with new onset of HTN and elevated renin and aldosterone levels with a h/o COVID-19.

Case Description: An 18-year-old Caucasian man with a remote history of asthma initially presented to his primary care physician with new onset of headaches. He was noted to have an elevated blood pressure, but otherwise a benign physical examination. A workup for secondary HTN revealed an elevated renin (8.7 ng/mL/hr), aldosterone levels (42 ng/dL) and otherwise unremarkable. He was started on Enalapril 5mg daily. A workup including CT and MRI of the brain, were unremarkable. He was referred to nephrology for the new diagnosis of HTN and abnormal renin and aldosterone levels. During the initial renal evaluation, patient was asymptomatic and his BP was well controlled on the Enalapril. Renin and aldosterone levels were repeated, about 8 weeks after the cessation of Enalapril. Patient’s blood pressure remained well controlled and didn’t require any medications. Since the diagnosis of HTN, the patient maintained a strict low salt diet. He always had good fluid intake. At a follow up visit, patient continued to remain asymptomatic and with good blood pressure control without needing medications. Repeat renin (1.9 ng/mL/hr) and aldosterone (16.8 ng/dL), as well as aldosterone/renin levels were resulted within normal limits. Patient admitted that he was diagnosed with COVID-19 6 months prior to his onset of headaches.

Discussion: SARS-CoV-2, which causes COVID-19, is known to hijack the RAAS cascade and use ACE2 enzyme to make human cell entry. Studies have demonstrated the possible correlation between COVID severity and comorbidities such as HTN (potentially involving the RAAS). Current recommendations are to continue the use of ACE Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) in COVID-19 patients. Our case, not only supports the above findings, but also demonstrates how RAAS is vulnerable to SARS-CoV-2, can manifest with new onset HTN and other complications. It is also interesting to see, how ACEIs and ARBs should be utilized as first line agents for BP control and to improve outcomes. To much relief, the effect on RAAS by the SARS-CoV-2 seems to be transient and short lived.
Page Kidney and Uncontrolled Hypertension: Rare Complication Post Kidney Biopsy

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Introduction: Page kidney is a rare phenomenon defined as an external compression of the renal parenchyma that can lead to hypertension and acute kidney injury. Compression of the renal parenchyma can occur from the formation of a subcapsular hematoma of traumatic or non-traumatic origin. This phenomenon can be seen as a rare cause of hypertension related to subcapsular hematoma formation following kidney biopsy. We report a case of a 34-year-old male with chronic kidney disease who developed abdominal pain and uncontrolled hypertension within 24 hours of kidney biopsy, found to have imaging findings consistent with Page kidney as a complication of the procedure.

Case Description: A 34-year-old male patient with a history of HTN, CAD, and stage 3B CKD presented to the ER with left flank pain and hypertensive urgency with SBP > 200 mmHg one day following a native kidney biopsy. He underwent a kidney biopsy for evaluation of sub-nephrotic range proteinuria and unclear etiology of CKD. CT abdomen/pelvis with contrast demonstrated a new 3.5 cm left subcapsular hematoma with perinephric and retroperitoneal extension. Abdominal pain worsened and repeat imaging showed expansion of the hematoma up to 24.5 cm. Before, during, and after kidney biopsy, the patient had well-controlled HTN with SBP range in the 130-140s mmHg. The day following the biopsy, SBP had risen to over 200 mmHg. Given his recent biopsy, significant HTN, and expansion of subcapsular hematoma on imaging, Page kidney was identified as the culprit leading to uncontrolled HTN. He was admitted to the ICU and started on a nicardipine drip with improvement in BP. Interventional radiology was consulted, and the patient underwent a left renal angiogram showing active extravasation at the hematoma site, which was then embolized. The patient achieved adequate BP control and the nico agreement drip was successfully weaned off. He was then transitioned back to his home oral antihypertensives.

Discussion: Page kidney refers to a condition in which there is an external force compressing the kidney which results in decreased kidney perfusion manifesting in a state of ischemia. This activates the RAAS system leading to secondary hypertension. Although many cases have previously been reported, Page kidney remains an uncommon cause, especially over recent years, of uncontrolled secondary hypertension and acute kidney injury.

Non-suppressed Plasma Renin Activity in Primary Aldosteronism with Hypertensive Kidney Disease

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Introduction: Primary aldosteronism (PA) prevalence has been estimated at 4.7–25.5% of all hypertensive patients. Renin aldosterone ratio (ARR) serves as a widely used screening test. Elevated ARR with suppressed plasma renin activity (PRA) is considered a positive screening test which should be followed by confirmatory testing. There are cases when PRA is associated with non-suppressed PRAs as in our case.

Case Description: A 37-year-old African American female patient with a past medical history of chronic kidney disease stage 4 presented to the hospital with a complaint of severe headache for 2 days associated with nausea and vomiting. Physical exam was remarkable for tachycardia and elevated blood pressure at 190/110 mmHg. Notable labs include low potassium at 3.4 (3.5 – 5.0 mmol/L), elevated creatinine at 4.84 (0.40 – 1.00 mg/dL) with a baseline creatinine of 2.36 mg/dL. The patient had a recent history of kidney biopsy which was complicated by a subcapsular hematoma, which transitioned back to his home oral antihypertensives.

The case is significant in that it demonstrates the importance of considering lowering ARR cutoff for diagnosis of PA since PRA isn’t completely suppressed in these cases.

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Discussion: The finding of non-suppressed PRA despite elevated ARR complicated diagnostic process. Multiple case studies reported non-suppressed PRA in patients with PA, especially when associated with hypertensive kidney disease and arteriosclerosis. In our case, kidney biopsy showed glomerulocystosis with arteriopathy consistent with hypertensive kidney disease. We suggest focusing on ARR as a reliable screening for PA and not solely depend on the fact that PA is associated with suppressed PRA, especially in these cases. Another important point is to consider lowering ARR cutoff for diagnosis of PA since PRA isn’t completely suppressed in these cases.

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Novel Use of Daratumumab for Post-Hematopoietic Cell Transplant Membranous Nephropathy

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Introduction: Membranous nephropathy (MN) is the most common cause of glomerulopathy after hematopoietic cell transplantation (HCT), usually seen with grade 3a or 3b disease (WHO). Although remission frequently occurs upon immunosuppression, 20% of patients fail to respond and may progress to end stage renal disease. Here we report the rapid remission of a treatment resistant patient with membranous nephropathy (Dnab).

Case Description: A 16 year old female 1 year post-HCT for beta thalassemia major was started on ruxolitinib for oral GVHD. Three months later, she developed nephrotic syndrome. Renal biopsy shown MN. Serum and renal tissue were negative for PLAPR antibody. Ruxolitinib was changed to ibritinib in case MN was medication induced. She was treated with tacrolimus (tough 3 – 8 ng/mL), prednisone, losartan, atorvastatin, and 4 weekly rituximab infusions. Eight months into therapy, she failed to meet criteria for even partial remission. Time course and biomarkers of MN are in Figure 1.

Discussion: The mechanism of HCT-associated MN is incompletely understood. Its association with GVHD and often successful treatment with rituximab have implicated direct or indirect humoral activation as potential pathogenic mechanisms. The success of CD3-depletion with Dnab may imply allosreactivity production by resident plasma cells as a driver of refractory disease. Dnab may be a novel therapeutic option for HCT patients who are not responsive to traditional MN therapy.

Figure 1: Time course and biomarkers of MN after Dnab. *Urine collection 15 hours

PO1852
Identifying Patients with CKD Risk at the Time of Partial Nephrectomy


Background: The prevalence of chronic kidney disease is high among kidney neoplasm patients because of the overlapping risk factors. We aim to identify risk factors of eGFR decline in kidney cancer survivors post partial nephrectomy (nx).

Methods: All partial nx patients with neoplasm at Northwell Health were included (2018/7-2020/5, n=187). Clinical and histology parameters, including neoplastic and non-neoplastic pathology, were analyzed. Non-neoplastic assessment includes glomerulosclerosis(GS), interstitial fibrosis and tubular atrophy(IFTA), and a semiquantitative estimate of the severity of arterial and arteriolar sclerosis (AAS). Multivariate linear mixed model was performed. Independent variables included age, sex, hypertension, diabetes, baseline eGFR, tumor diagnosis, proteinuria, GS%, IFTA%, and AAS.

Results: The median follow-up time is 147d. In all patients, independent risk factors of post-nx decreased eGFR were female(=0.02), age(=0.01), overweight(=0.01), eGFR<90 at the time of nephrectomy(=0.001), severe AAS(=0.01), and prolonged follow-up. In the ones with baseline eGFR>90(=0.01) and eGFR<90 at the time of nephrectomy(=0.001), severe AAS(=0.01), and prolonged follow-up. In patients with baseline eGFR<90 and eGFR<90(=0.02), severe AAS(=0.02), and overweight(=0.03) were independent risk factors of decreased post-nx eGFR.

Conclusions: We propose a minimum workup for this population to include eGFR, urinalysis, and non-neoplastic pathology evaluation. The time of kidney cancer treatment may be a unique opportunity for these patients to be identified and directed to early interventions, including nephrology consults and patient education on nutrition and weight control.

PO1853
Development of 3D Renal Cell Carcinoma Organoids and Cancer Invasion Assay

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Background: Recent advances in vitro 3D culture technologies, such as organoids derived from hPSCs, have opened new avenues for development of human disease models. Modeling cancer by utilizing cancer organoids provides advantages as they maintain 3D cell–cell interactions, heterogeneity, microenvironment, and drug response of the sample they originate from. Such preclinical models are essential for more efficient translation of cancer research into novel treatment regimens for patients. 5-year survival rate at advanced stage IV RCC is less than 10%, as RCC is also notorious for resistance to chemotherapy and radiation therapy. Therefore, development of effective tools for better understanding and drug screening for RCC are needed. Kidney cancer organoids and novel assays such as cancer invasion assays can be useful tools to personalize potential therapeutics.

Methods: Primary kidney cancer cell lines were generated from patient biopsy samples. 3D kidney cancer organoids and non-cancer kidney organoids for cancer invasion assay were generated from primary kidney cancer cell lines and hPSCs, respectively, by modifications of our laboratory’s prior published kidney organoids techniques. Organoids were characterized by immunostaining. Upon maturation, organoids were added onto the cancer organoids by the receptor tyrosine kinase inhibitor, sunitinib or the histone acetyltransferase inhibitor (A-485) showed reduction in efficacy of cancer invasion. The cancer organoids showed significantly better expression of kidney specific markers (vimentin) compared to 2D primary cultures. The invasion of cancer organoids was assessed using an invasion assay. The invasion of organoids increased in the presence of a chemokine receptor antagonist. The invasion of organoids was reduced using siRNA to knockdown a chemokine receptor. The invasion of organoids was increased in the presence of a chemokine receptor antagonist. The invasion of organoids was reduced using siRNA to knockdown a chemokine receptor.

Results: RCC cancer organoids showed significantly better expression of kidney specific markers (vimentin) compared to 2D primary cultures. The invasion of organoids increased in the presence of a chemokine receptor antagonist. The invasion of organoids was reduced using siRNA to knockdown a chemokine receptor. The invasion of organoids was increased in the presence of a chemokine receptor antagonist. The invasion of organoids was reduced using siRNA to knockdown a chemokine receptor.

Conclusions: These results demonstrate the potential of 3D cancer organoids for development of effective tools for better understanding and drug screening for RCC are needed. Development of cancer invasion assays can be useful tools to personalize potential therapeutics.
PO1854
Multi-Omics Approach to Uncover Underlying Biology of Low-Risk Clear Cell Renal Cell Carcinoma Patients with Progressive Disease
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Background: Renal Cell Carcinoma (RCC) constitutes approximately 3% of all cancers and its incidence is rising worldwide, especially in Western countries. In the last two decades, enormous advances have been made in the development and implementation of medical therapies for metastatic ccRCC, however, surgery still represents the only curative option. One of the issues in developing a curative medical therapy lies in the high degree of inter-, and intra-tumor heterogeneity. We believe that by applying multi-omics technology to highly specific subgroups and comparing them to closely matched controls we can mitigate the heterogeneity issue and deepen our understanding one step and subgroup at the time.

Methods: We assembled a cohort of ccRCC patients (n=443) and identified all “low-risk” patients which later developed progressing tumours (n=8). Subsequently we performed genome-wide expression profiling, miRNA profiling and proteomics profiling from formalin-fixed samples obtained at initial surgery from these “low-risk” patients and 16 matched patients not progressing to recurrence with metastasis. The patients were matched for Leibovich stage, age, sex, tumor size and tumor stage.

Results: Pathway analysis yielded differences between progressive and non-progressive patients in categories such as Molecular Mechanisms of Cancer, B Cell Receptor Signaling in mRNA data and Acute Phase Response Signaling and FXR/RXR Activation in proteomics data. By integrating our three omics analysis we revealed that acute Phase Response Signaling also plays a role on all three levels. Additionally, we developed a 14-component classifier, drawing from both mRNA, miRNA and protein-based data that reliably differentiated the different subgroups. We further examined the correlations between each of the components and uncovered a dense network of interactions.

Conclusions: Multi-omics methods represent an important tool in furthering our understanding renal cancer biology in the pursuit of medical therapies.

PO1855
TMEM27 Expression and Clinical Characteristics and Survival in Clear Cell Renal Cell Carcinoma
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Background: Transmembrane protein 27 (TMEM27/collectrin), a glycoprotein and homolog of angiotensin converting enzyme 2 (ACE2), is a regulator of renal amino acid uptake in the proximal tubule and may have a protective role in hypertension. Previous reports have shown that the absence of TMEM27 expression in clear cell renal cell carcinoma (ccRCC) correlates with poorer cancer-related survival. Here we report our findings of TMEM27 expression in ccRCC and clinical outcomes.

Methods: We conducted a retrospective analysis to identify all cases of ccRCC diagnosed between 2010 and 2015 at the University of Rochester Medical Center. The intensity of TMEM27 immunostaining on tumor tissue was semi-quantitatively graded on a scale of 0, 0.5, 1, 1.5, 2, 2.5, and 3 by a single pathologist, and correlated with tumor characteristics and survival.

Results: There were 321 cases of ccRCC. There was evidence of metastasis at time of nephrectomy in 36 (11.2%), and at the latest follow up in 70 (21.8%), and 82 (25.5%) died as of Spring 2021. TMEM27 staining intensity correlated inversely with various clinicopathologic characteristics (Table 1). Kaplan-Meier survival analysis showed worse all-cause mortality for tumors without any TMEM27 staining (0) compared to 0.5 or higher, p = 0.02 by log-rank test.

Conclusions: The absence of TMEM27 expression is associated with more aggressive tumor characteristics and poorer all-cause mortality in ccRCC. TMEM27 may be a useful biomarker to assess cancer prognosis. Further studies are needed to better assess if TMEM27 is protective in RCC.

Table 1: Correlation between TMEM27 Staining and Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>≤0.5</th>
<th>&gt;0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor stage (pT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pT1a)</td>
<td>-0.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(pT3)</td>
<td>-0.125</td>
<td>NS</td>
</tr>
<tr>
<td>Prognostic grade</td>
<td>-0.187</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Surgery (partial vs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>radical)</td>
<td>-0.073</td>
<td>NS</td>
</tr>
<tr>
<td>Lymph node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(present)</td>
<td>-0.133</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>-0.072</td>
<td>NS</td>
</tr>
<tr>
<td>Metastases at time of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nephrectomy</td>
<td>-0.126</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age</td>
<td>0.208</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid with diabetes</td>
<td>-0.201</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PO1856
Role of miR-23b and miR-133a in Apoptosis Control Induced by TRAIL in Lung Adenocarcinoma and Kidney Carcinoma Cell Lines
Denise Leite, Edgar Maquigussa, Mirian A. Boim. Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil.

Background: Lung and kidney cancer are often diagnosed as advanced disease and frequently become resistant to systemic therapies. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) binds to TRAIL receptor 1 and 2 (TRAIL-R1/R2) on the cell surface to stimulate apoptosis, making TRAIL apoptotic pathway a promising target for cancer therapy. Cullin-3 ubiquitination is essential to TRAIL receptors activation. However, resistance to TRAIL is an obstacle to achieve an effective anti-tumoral therapy. One of the mechanisms that lead to TRAIL resistance appears to be dependent on translocation, mediated by clathrin (CLTA), of TRAIL receptors to the nucleus. MicroRNAs (miRs)-23b and -133a may have relevant role in TRAIL resistance.

Methods: A549 and CaKi-2 cell lines and their respective controls (MRC-5 and HK2) were used. mRNA expressions of miR-23b, miR-133a, TRAIL-R1/R2, CUL3, CLTA, Apaf1 and KPNA-1 were estimated by RT-qPCR. MIT assay was used to evaluate the effect of TRAIL-induced cytotoxicity. TRAIL receptors cellular distribution was determined by western blot.

Results: Both cell lines were TRAIL resistant on MTT. TRAIL-R1 and TRAIL-R2 were predominantly located in nuclear compartment of A549 cells. TargetScan showed that miR-23b targets CUL3, Apaf1 and KPNA-1 and miR-133a targets CLTA. MiR-23b expression was upregulated in A549 and CaKi-2 cells. MiR-23b inhibition upregulated CUL3 expression in A549 cells. In contrast, miR-133a was undetectable in both cell lines. TargetScan was used to determinate potential mRNA targets for miR-23b and miR-133a.

Conclusions: MiR-23b expression was upregulated in A549 and CaKi-2 cells. However, supposed miR-23a target mRNAs were unchanged suggesting no relationship between miR-23a and those molecules. MiR-23b inhibition upregulated CUL3 expression in A549 cells, which could enhance TRAIL receptors activation and sensitivity- this will be investigated in next step. In contrast, miR-133a was undetectable raising the hypothesis of an increased capacity of cells to translocate TRAIL receptors to the nucleus via clathrin and thus be resistant to TRAIL. The possible miR-133a ability to reduce clathrin expression may represent a novel approach for control of TRAIL apoptotic pathway and must be further investigated as a TRAIL sensitizing mechanism.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1858

Characterization of Wilms Tumor and Human Fetal Kidney Using Spatial Transcriptomics

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Background: Growing evidence links Wilms tumor (WT) to aberrant nephrogenesis. Studies highlighted the genetic complexity of WT, but little is known about the molecular mechanisms that regulate WT development. Using Spatial transcriptomics (ST), which allows analysis of the gene expression based on morphological context, we showed important differences between WT subtypes and defined the interactive gene networks involved in WT development using human fetal kidney (hFK) as reference.

Methods: Using Visium 10x Genomics, we generated spatial maps of gene expression in human fetal kidney (hFK) and favorable (stage III) and unfavorable (stage I) WTs. Data were analyzed using Space Ranger software v1.0.0, Seurat v3.2, Panther V14, and Loupe Cell Browser and further analyzed against our previously generated bulk/sc-RNA seq data on the same samples.

Results: ST identified specific clusters in hFK that closely recapitulated the developmental stages of normal nephrogenesis (nephrogenic zone, glomeruli, tubules, and stroma). Unfavorable WT and favorable WT clusters showed heterogeneity of the tumor landscape (blastema, epithelium, and stroma and non-renal phenotypes). Blastema in WT favorable vs. WT unfavorable, though histologically identical, presented different transcriptionomics profiles. WTs also showed gene expression typical of muscle tissue (or other non-renal phenotypes) rather than mature kidney structures, which correlated with the histologic absence of mature tubules and glomeruli. Comparative RNA-seq analysis identified cells expressing SIX2 and CITED1 as the root cells of the origin of the WT. Unfavorable WT expressed a higher level of CITED1 in blastema foci and higher expression of uncommitted genes and modulation of inductive nephrogenic signals like WNT and FGF. We also identified genes expressed specifically in WT subtypes and performed a preliminary characterization of the immune milieu of WT.

Conclusions: The spatiotemporal mapping combining with different transcriptionomic data highlighted the heterogeneity of the WT subtypes confirming uncommitted nephron progenitors as driving the development of WT. We identified genes that may allow for better stratification of WT and potential therapeutic targets for distinct WT subtypes.

Funding: Private Foundation Support

POI1859

Recurrent Renal Cell Carcinoma Post Renal Transplantation

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Introduction: Renal Cell Carcinoma (RCC) can occur in renal transplant recipients (RTR). RCC recurrence post nephrectomy occurs in 20-40% of non-transplant(Tx) patients and in less than 15% of RTR. The median survival for patients with metastasis is 6-12 months with 5 year survival less than 10%. We present 3 RTR who developed recurrent RCC post-Tx.

Case Description: RTR1 was 61 years old and received a deceased donor kidney Tx (DDKTx) for IgA nephropathy. He was induced with thymoglobulin. Immunosuppression(IS) included Mycophenolate Mofetil (MMF), Tacrolimus (FK), and steroids (S). 8 years pre-Tx, a 2.5cm RCC lesion was found in the R native kidney, and he underwent nephrectomy. 1 year later, he developed BK viremia, and IS was changed to Everolimus and S. 2 years post-Tx, RCC metastasis was detected only in the pancreas head and tail. Treatment involved tyrosine kinase inhibitors(TKI) and VEGF inhibitors without resolution; he died within 2 years of RCC recurrence with a functioning allograft. RTR2 was 56 years old and received a DDKTx, secondary to APD. IS involved MMF, Cyclosporine, and S. History was significant for L nephrectomy 3 years pre-Tx for RCC. Both lesions were small and renally limited. 10 years post Tx, she presented with recurrent RCC in the pancreas and thyroid. Treatment involved change in IS to Sirolimus and Azathioprine. No other treatment was taken by the patient. She died 4 years later with a functioning allograft. RTR3 is a 54 years-old who received a living, related renal Tx for CKD stage 5. IS included MMF, FK, and S. 8 years post-Tx, he was diagnosed with an 8cm RCC lesion of the L native kidney and underwent nephrectomy. After a 6 year tumor free interval, RCC recurred only in the lungs and lymph nodes. He received IS reduction and TKI with progression of disease to bone metastasis. His current treatment involves TKI with Dosemab, and he still has a functioning allograft.

Discussion: Our cases demonstrate that RCC recurrence occurs at variable time points post-Tx and can present aggressively in RTR with poor outcomes. We suspect that recurrent disease arises from micrometastatic tumor cells that escape immune surveillance. RTR with a history of RCC prior to Tx should be monitored closely for metastatic recurrence post Tx.

POI1860

Impact of ESKD on Overall and Cancer-Specific Mortality in Patients with Localized Prostate Cancer (PCa): A Retrospective Cohort Study of SEER-Medicare

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Background: Our objective was to compare overall and PCa specific mortality between ESKD and non-ESKD patients with localized PCa.

Methods: Study participants were male patients, who were diagnosed with localized PCa between January 1st 2004 and September 30, 2015 (last day of International Classification of Diseases-9-Clinical Modification (ICD-9-CM) use) and were 40 years or older at the time of diagnosis. ESKD status, further stratified into dialysis and kidney transplant (KT) was determined using ICD-9-CM codes. Time to death from any cause was modeled using Cox regression and time to PCA specific death using Fine and Gray competing risk model.

Results: At a median follow up of 6.2 years, 3.5 years and 5.0 years for non-ESKD (N=186,482), dialysis (N=970) and KT (N=413), overall mortality rates were 1.8%, 8.5%, and 4.8% at 1-year, 7.7%, 31.5% and 13.5% at 3-years and 15.2%, 50.8% and 27.9% at 5-years respectively (P-Value: <0.001), Figure 1. In multivariate model, dialysis status was associated with 2.9 times higher hazard of death (HR: 2.9) and transplant status was associated with 2 times higher hazard of death (HR: 2.0) compared to non-ESKD group. Rates of PCa specific mortality were 0.4%, 1.1%, and 0.7% at 1-year, 1.6%, 3.1%, and 1.5% at 3-years and 3%, 4.8%, and 2.2% at 5-years for non-ESKD, dialysis, and transplant groups respectively (P-value: 0.04). In multivariate model, dialysis status and transplant status were associated with similar risks for PCa specific death to non-ESKD group, Figure 2.

Conclusions: ESKD patients have excess relative overall mortality but similar PCa specific mortality compared to non-ESKD patients with localized PCa.

POI1861

Case of Spontaneous Tumor Lysis Syndrome in Metastatic Prostate Cancer

Mohammad Al-Hasan, Mauricio Monroy, Albany Medical Center, Albany, NY.

Introduction: Tumor lysis syndrome has been described in hematological malignancies mainly where there is a large tumor burden that lyse in relatively short period of time causing a large burden of metabolites that causes AKI. In this case, we will present a case of spontaneous tumor lysis syndrome caused by widespread metastatic cancer prostate which is an unusual cancer to cause such syndrome. That metastasis was mainly to the bone marrow causing a picture of pancytopenia, which also raises the possibility that the tumor lysis syndrome could be due to the breakdown of the cells of the bone marrow rather than the lysis of the prostate cancer cells.
Case Description: 65-year-old male patient presented with altered mental status up to 5 days. He had 5.2, severe anemia of 7.2 g/dL, and a creatinine of 7.32 and BUN of 181, calcium 9.3, phosphorus 7.4, uric acid 41.5, bilirubin of 2.9 and LDH was high at 789, alkaline phosphatase was 345, patient had severe anemia with hemoglobin of 2.6, white count 12,600 and thrombocytopenia with platelet count of 190,000. Serum analysis showed uric acid crystals. Flow cytometry analysis of peripheral blood did not reveal a clonal population of cells or expanded population of blasts. CT scan chest abdomen pelvis suggested diffuse osseous lytic and blastic metastatic lesions. Serum immuno-electrophoresis was negative. PSA level of more than 1400.

Diagnosis: The patient along with a low elevated serum uric acid level, and presence of uric acid crystals in the urine sediment, made it likely the diagnosis of TLS. The presence of diffuse osseous lesions and a PSA above the level that can be measured were consistent with metastatic prostate cancer as the underlying malignancy. The initial treatment was obtained TLS in solid malignancies was rare, especially without anti-neoplastic therapy. In this case, the presence of severe anemia and thrombocytopenia were highly suspicious for bone marrow invasion, and possible contributor to TLS. Regrettably, a bone marrow biopsy couldn’t be obtained before patient expired. Conclusion: Bone marrow extension with loss of bone marrow cells maya be a contributing factor.

PO1862

Overlooked and Unanticipated: Life-Threatening Hypocalcemia due to Denosumab in a Patient with Prostate Cancer

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Introduction: Denosumab is a monovalent antibody that inhibits osteoclast-mediated bone resorption by binding to receptor activator of NF-κB ligand, which is upregulated by tumor cells. Despite FDA warning, insidious and severe onset hypocalcemia is a malignant and overlooked complication in patients with advanced CKD.

Case Description: A 77-year-old man with a history of prostate cancer and CKD stage 4 presented to the ED with tremors and numbness in both arms along with perioral dysesthesia. In addition to furosemide and metoprolol, he received his first dose of denosumab 2 weeks prior to presentation, indicated for bone metastases. Physical examination was remarkable for the Chvostek sign and delayed reflexes in the upper and lower extremities. Lab results were as follows: Na 136 mEq/L, K 4.4 mEq/L, Cr: 4.8 mg/dL, PO4: 6.1 mg/dL, Ca: 4.8 mg/dL, Mg: 2.6 mg/dL & albumin: 3.5 g/dL. Further testing revealed a serum 25(OH) vitamin D of 6.5 (25 ng/mL). IPTH: 988 (10-55 pg/mL). C-teropeptide: 167 (40-465 pg/mL). ALKPh: 243 (44-147 IUL). Urine calcium-to-creatinine ratio was 0.04, suggestive of minimal calcium excretion. ECG showed prolonged QTc. Given the clinical evidence of severe hypocalcemia and ECG changes, the patient was started on peripheral calcium infusion with hourly iCa2+ measurements to maintain iCa>1 mmol/L and reversal of QTc prolongation. Concomitantly, the patient was treated with calcium carbonate 2500 mg TID, ergocalciferol 50,000 units weekly, and calcitriol 0.5 mcg BID. After 72 hours, his ionized calcium levels stabilized with aggressive oral therapy only. Serum calcium at discharge was 8.2 mg/dL and remained low in the range of 7.5-8.9 for the following 8 weeks.

Discussion: Denosumab has a prolonged elimination half-life (up to 32 days) and therefore, it can induce severe & relapsing hypocalcemia, especially in patients with low vitamin D stores. While patients with creatinine clearance <30 mL/min have been found to be prone to adverse effects, no dose modification has been considered for this therapy. Our study suggests that low-normal protein high calories diet ameliorates the nephrological scenario, the metabolic complications and the nutritional perspective in uro-oncological CKD pts. Following NNCA, perceived quality of life has been pushed towards high scores and does not appear to be influenced by physical health. The nutritional status and quality of life improved. Close monitoring and food counseling will be necessary if malnourished patients have increased the perception of the pathological condition, thereby increasing the sense of responsibility in adhering to the NT. All this improves the physical health, but also demotivates pts and worsens their social attitudes.

PO1863

Impact of CKD on the Nutritional Status of Patients with Cancer

Micheline T. Souza,1 Luiz A. Gril,2 Thais d. Cardenas,3 Renato A. Caires,2 Elerson Costalonga,1 George B. Coura-Filho,1 Marcelo T. Sapienza,1 Lesley A. Inker,1 Andrew S. Levey,1 Emmanuel A. Burdman,2 Veronica T. Costa e Silva,1,2,3 University of Sao Paulo Medical School, Sao Paulo, Brazil; 2Sao Paulo State Cancer Institute, Sao Paulo, Brazil; 3Tufs Medical Center Cancer Center, Boston, MA.

Background: Cancer patients routinely live with impaired nutritional status and other comorbidities. There are few prospective data on the impact of chronic kidney disease (CKD) on the nutritional aspects of patients with cancer.

Methods: Patients with solid cancer, admitted for treatment at a cancer hospital in Brazil (Instituto do Câncer do Estado de São Paulo) were prospectively evaluated between April 2016 and October 2017. Patients underwent a nutritional evaluation including subjective global assessment produced by the patient (PG-SGA), anthropometry (Arm Muscle Area-AMG, weight, height) and electrical bioimpedance (BIA). sarcopenia was defined according to cutoffs of 3.26 m²/kg in men and ≤17.46 m²/kg in women. Measurement of the glomerular filtration rate was determined through plasma clearance of [125I]-ETDA (mGFR). CDC was classified according to the KIDG cut-offs based on mGFR indexed for body surface area.

Results: Six hundred and ninety-six pts were enrolled. Patients were 60(51-67) years range, 51.9% male. The most common cancer sites were breast(26.3%), prostate(20%), and gastrointestinal(12.2%). A total of 14.7% had metastatic disease, 94.9% ECOG 0, 2% ECOG 1. Median mGFR was 81. (66.7-94.6), with 55.7%, 32.8% and 11.5% presenting mGFR G1, G2 and G3, respectively. When compared to patients with mGFR G1, patients with mGFR G2 and G3 had a higher frequency of malnutrition by PG-SGA and BMI, and a higher prevalence of sarcopenia according to AMB. In addition, fat free mass deficit, sarcopenia and lower phase angle values were more frequently observed in mGFR G2 and G3 according to the BIA data(Table1).

Conclusions: In patients with cancer admitted for treatment lower mGFR was associated with worse nutritional status. Therefore, nutritional monitoring in conjunction with the oncology, nephrology and nutritional team is necessary.
Timeline of Events

**PO1866**

Kidney Pathology Findings in Patients with AKI Associated with Tyrosine Kinase Inhibitors

Venkata Kishore R. Mukku,1, 2 Omar Mamlouk,2 William F. Glass,1 Amanda Tchakarov,1 Sreedhar Reddy,1, Jatinder Kohli.

1, e Regional Medical Center, Atlantic City, NJ; 2The University of Texas Health Science Center at Houston, Houston, TX; 3The University of Texas MD Anderson Cancer Center, Houston, TX; 4The University of Texas Health Science Center at Houston, Houston, TX.

Background: Tyrosine kinase inhibitors (TKIs) are widely used targeted cancer therapy and play a critical role in the modulation of growth factor signaling. Nephrotoxicity associated with TKIs can lead to interruption of therapy. However, the literature on the kidney pathology associated with TKIs nephrotoxicity is limited. Here, we present our center observation of tubular and glomerular lesions attributed to possible TKIs.

Methods: We retrospectively reviewed all cancer patients from 2018 to 2020 who were treated with TKIs and underwent a kidney biopsy at the University of Texas MDACC.

Results: We identified 13 cancer patients treated with Sunitinib, Cabozantinib, Levatinib, Regorafenib, Erlotinib, Osimertinib and Ibrutinib between 2018-2020 and developed acute kidney injury (AKI) attributed to possible TKI nephrotoxicity. The median age was 70 (range, 43 to 80) and the median time to develop AKI was 4 months (range, 1 to 58 months) of starting TKI. AKI was severe (stage ≥ 3) in 6 patients, among which 4 required hemodialysis. Most of the patients had bland urine (7 out of 13) and proteinuria was observed only in 6 patients. Thrombotic microangiopathy (TMA) was the most common pathological finding followed by acute tubular injury (ATI) as they were observed in 5 and 4 patients, respectively. One patient had proliferative glomerulonephritis, one patient had chronic lymphocytic leukemia infiltration, and one patient had no active lesion. TKIs were discontinued in nine patients, and nine patients had partial kidney recovery. Five patients had disease progression and died within 4 months of AKI.

Conclusions: Our case series has demonstrated that kidney limited TMA and ATI are common pathology findings in patients with suspected TKI nephrotoxicity. Nonetheless, half of patients with TMA were on concurrent checkpoint inhibitor therapy with TKI and half of the patients with ATI had associated sepsis diagnosis. The mechanism is likely multifactorial and possibly related to mTOR and VEGF inhibition leading to endothelial injury, and inhibition of the downstream signaling pathway of MAPK/ERK1/2 leading to ATI. Urine analysis was not predictive of the kidney pathology. Treating nephrotoxicity by discontinuation of the offending TKI was associated with partial kidney recovery, however patients had poor overall prognosis.

**PO1867**

Renal Pathology in Cancer Patients in a New Era of Treatments

Mónica Bolufer,1 Clara García-Carro,1 María Jose Soler.1 On behalf of the GLÓSSEN ONCONEFROLOGÍA,2 Vall Hebron, Barcelona, Spain; 3Hospital Clínico San Carlos, Madrid, Spain.

Background: Classically patients with metastatic cancer were not submitted to invasive procedures because of their short life expectancy. Kidney biopsy(KB) is an especially useful diagnostic and prognostic tool in these patients when they develop kidney injury. The aim of our study is to assess clinical and histological characteristics of patients with active solid organ malignancy that underwent KB in a multicenter cohort.

Methods: We performed a multicenter collaborative study. Clinical, demographic and pathological data from patients with an active neoplasia or kidney cancer treatment who underwent KB were collected. We studied the follow-up in the patients in terms of renal function and survival.

Results: 124 patients with cancer who underwent KB during the study period from 2015-2019 were included. The median age was 63.0 years (range 11-91 years). The indications of KB were acute renal failure (56.2%), proteinuria (20.2%) and exacerbation of CKD (15.3%). At the time of the KB, 30.6% patients presented diabetes and 63.7% high blood pressure. Malignancies: lung (30.6%), intestinal (27.4%), melanoma (7.3%) and unknown primary (17.7%). When the metastatic malignancy 35.5% received chemotherapy, 31.4% immunotherapy (of which 26.3% received more than 1 checkpoint inhibitor), 24.2% specific therapies and 3.2% conservative treatment Baseline renal function before KB,16.1% presented Cr=1.5mg/dL. At the time of KB, mean Cr 2.55/mg/dL [1.7-3.97] (25-75), urine protein/Cr ratio 895mg/gCr (5.25) and 53.2% hematuria KB diagnosis:35.5% acute interstitial nephritis (AIN), acute tubular necrosis(8.9%) and IgA nephropathy(8.1%).65% of patients received corticosteroids for an average of 4 months[SD ± 3.9] 20.2% required kidney replacement therapy and 36.3% presented Cr=1.5mg/dL at 3 months. Average follow-up[16.2±5.3-32.8] (Q 25-75)=12 months. 37.9% died at the end of the follow-up and the moment of KB was identified as an independent risk factor for mortality (p=0.012)

Conclusions: Currently, AIN is the first cause of kidney injury in biopsied patients with active cancer. This is followed by membranoproliferative glomerulonephritis (MPGN), membranous nephropathy and IgA among others. KB in this group of patients provides valuable diagnostic and prognostic information. More studies are needed to expand the consensus in the diagnosis and treatment of oncological patients with renal injury.

**PO1868**

Treatment of PLA2R-Negative Membranous Nephropathy in the Setting of Immune Checkpoint Inhibitor and Renal Cell Carcinoma

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Introduction: Systemic therapy of renal cell cancer (RCC) has undergone major changes over the past decade with the development of targeted therapies such as tyrosine kinase inhibitors (TKIs) and biologic therapies such as immune checkpoint inhibitors (ICIs). Familiarization of the unique nephrotoxicity associated with each treatment is necessary to optimize renal outcomes and cancer care.

Case Description: 57-year-old male with metastatic RCC s/p left nephrectomy progressing after being treated for 16 weeks with the TKI axitinib in combination with pembrolizumab, an ICI targeting PD-1. He subsequently progressed after a 14-week course with second-line cabozantinib (TKI) and pembrolizumab, an ICI targeting PD-1. He achieved a complete response (mTOR inhibitor) two months prior to presenting with severe diarrhea. Labs were notable for creatinine (Cr) of 2.28 mg/dL (baseline 0.96 mg/dL). CT revealed suspicion for colitis and decreased tumor size of his metastatic disease. Further work-up revealed: 2.87 g on 24 h urine protein, negative anti-GBM and ANCA antibodies, and normal complements. Renal ultrasound showed a hypertrophic right kidney measuring 14 cm in length without obstruction. Due to the broad AKI differential, steroids were empirically started for possible immune-mediated disease, and biopsy was obtained. Pathology revealed membranous nephropathy (MN) with mesangial deposits, PLA2R and THSD7A were negative. While worsening renal function with Cr 3.87 mg/dL risk for progression to dialysis, treatment with rituximab (1 g IV D1 and D4) was initiated. Follow-up labs at one month showed Cr 1.50 mg/dL and the patient was restarted on levatinib and everolimus with continued durable response.

Discussion: While TKIs may induce TMA and mTOR inhibitors have been associated with proteinaemia and ATN, our patient revealed a unique presentation of secondary MN that was likely induced by his relatively recent ICI therapy. MN can also present as a paraneoplastic lesion, but it is rarely associated with RCC and the presentation did not correlate with his improved CT scan. Given his deteriorating kidney function, treatment with rituximab was fortunately successful and allowed for continued treatment with durable cancer response.

**PO1869**

Primary Adrenal Insufficiency Secondary to Immune Checkpoint Inhibitors

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Introduction: ICIs are humanized or human immunoglobulin antibodies. Administration of a monoclonal antibody that interrupts the interaction between PD-L1 and PD-L2 and the T-cell PD-1 receptor allows tumor-infiltrating lymphocytes (activated T cells) to aggressively identify and destroy cancer cells. However, use of ICIs can result in so-called immune-related adverse events (IRAEs). We present a case of a 55 year old male with history of metastatic malignant melanoma who presented with ICI induced adrenal insufficiency.

Case Description: 55-year-old male PMH of HTN, COPD, Hypothyroidism, metastatic malignant melanoma was recently started Nivolumab presented to the ED with altered mental status and confusion. Laboratory values were notable for hypoglycemic (46mg/dl), hyponatremia (124mmol/l) and borderline High K (5.5mmol/l), serum osmolality 256 mosm/kg and urine osmolality 538 mosm/kg. He was initially treated with IV dextrose. Serum cortisol and ACTH were checked to rule out adrenal insufficiency
as etiology for above laboratory abnormalities and history of treatments with ICI (nivolumab), while awaiting these lab results, patient was started on fluid restriction and salt tablets for management of hyponatremia based on available labs at that point which pointed to hypotonic hyponatremia with high urine osmolality pointing to ADH release and goal for correction for sodium level maintained 6-8 Meq for 24hours. Both serum cortisol and ACTH levels were low with values of 1.4ug/dl and 3.5pg/ml respectively. Patient was subsequently started on IV fluids and IV hydrocortisone 100 mg. Serum sodium level improved at an appropriate rate during the course of hospitalization and serum sodium at the time of discharge was in safe range (136mmol/L). Other peripheral hormones including prolactin, GH, TSH, LH and FSH which were normal. MRI Brain was done to rule out hypophysitis which revealed normal sella.

Discussion: Long-term follow-up of endocrine irAEs suggests that on occasions thyroid function may recover, but that dysfunction of the corticosteroid and gonadal axis is likely to be permanent. Patients should be informed of the potential adverse events prior to initiation of immune checkpoint inhibitors. Laboratory findings similar to our patient should raise concern for adrenal insufficiency to allow timely diagnosis and management and thus prevent morbidity and mortality.

PO1870

Immune Checkpoint Inhibitors Associated Distal RTA with and Without AKI

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Introduction: As immune checkpoint inhibitors (ICI) gain popularity as a widely used anti-cancer therapy, unique immune-related adverse events (irAE) are being associated with their use. Hereby, we present two cases that link ICI therapy to distal RTA, one with and one without AKI.

Case Description: A 73-year-old male with urothelial cancer on pembrolizumab was evaluated for AKI and acidosis. After 5 doses of ICI therapy, he was noted to have a serum creatinine of 1.88mg/dl (normal baseline) and a serum CO2 of 20mmol/L. Over the next few days, the serum CO2 further decreased to 11mmol/L and serum potassium declined to 3.0mmol/L. Further workup revealed a urine pH of 6.5 with a positive urine anion gap. He was diagnosed with likely ICI-induced AKIN with distal RTA and initiated on sodium bicarbonate, potassium citrate, and prednisone 60mg/day. His ICI was held. After 2 weeks of treatment, his serum creatinine returned to 1.2mg/dl and serum CO2 to 22mmol/L. A 46-year-old female was diagnosed with metastatic lung cancer and squamous cell carcinoma of the right tonsil for which she was initially treated with Carboplatin/Paclitaxel/Pembrolizumab followed by maintenance Pembrolizumab. Almost 3 months after being initiated on ICI, she was noted to have normal gap metabolic acidosis that gradually worsened to serum CO2 of 15mmol/L along with serum potassium of 2.4meq/L and serum creatinine of 0.6 mg/dl. Further workup showed a urine anion gap of -26, urine osmolar gap of 80, urine pH of 6.0. 24-hour urine citrate was undetectable. Diagnosis of distal RTA secondary to pembrolizumab was made and therapy was held. Steroids were not initiated, as the kidney biopsy, performed within 2 months of holding the therapy, did not reveal any tubulitis or cellular infiltrates. She is being treated with potassium citrate with normalization of acidosis and hypokalemia.

Discussion: We describe two cases of distal RTA presenting as immune related adverse events associated with use of ICI. AKI presence is not necessary. Prompt recognition of the need to quickly taper ICI has been paramount. It has been postulated that a difference in the expression of PD-L1 among the tubular epithelial cells is responsible for isolated distal RTA.

PO1871

Immune Checkpoint Inhibitor-Associated Electrolyte Disorders: Query of the FDA Adverse Event Reporting System

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Background: Electrolyte disorders with immune checkpoint inhibitors (ICI) therapy are not well characterized. Single center studies have noted hyponatremia as the most common electrolyte disorder associated with ICI (nivolumab). We performed a revised more recent query of the FAERS database with a more detailed look at electrolyte disorders only (search terms: hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypocalcemia, hypophosphatemia, hypomagnesemia, acidosis, hyperphosphatemia and renal tubular acidosis) from 2011-2021.

Results: A total of 2556 cases of electrolyte disorders were reported to the FAERS system. The most commonly reported abnormality is hyponatremia (53.7%), followed by hypokalemia (18.71%), hypercalcemia (9.65%), hyperkalemia (5.56%) and hypocalcemia at 4.04%. The remaining abnormalities were <4%. In all three groups of the agents (CTLA4 inhibitors, PD and PD-L1 inhibitors), the trend remained similar. Most events were reported at a median age of 64 in all 3 groups analyzed. Among reported events, proportions of events in male were statistically more significant (p<0.01) than females in all 3 drug groups. Nivolumab (n=1130) and ipilimumab (n=676) had more number of patients reported with electrolyte disorders. Hyponatremia persisted as the most common abnormality in each specific drug use. Hypokalemia and hypercalcemia were fairly common. Hyperphosphatemia, hyponatremia, hyperphosphatemia along with acidosis made up the least number of cases reported.

Conclusions: Electrolyte disorders are an under-recognized cause of ICI therapy. Hyponatremia, hypokalemia and hypercalcemia seem to be the three most commonly reported events with these classes of drugs.

Review of the Food and Drug Administration Adverse Event Reporting System database for adverse events related to electrolytes by gender by different medication classes.

PO1872

Immune-Checkpoint Inhibitor Use in Patients with ESKD

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Background: As use of immune check point inhibitor (ICI) therapy becomes increasingly widespread across different types of cancer, their use in patients receiving dialysis is likely to increase.

Methods: We performed a structured search of the MEDLINE and EMBASE databases from inception to February 2021. We sought to identify case reports, case series, observational studies and clinical trials which described the use of ICI therapy for cancer in patients receiving dialysis (either hemodialysis (HD) or peritoneal dialysis (PD)). For each included study, we performed a standardized patient-level data abstraction using pre-specified parameters of interest: patient demographics, cancer diagnosis, ICI treatment characteristics, dialysis modality, immune-related adverse events (irAE), cancer outcomes and survival.

Results: 136 citations for title and abstract screening were noted. Of these 33 met criteria for inclusion. 98 cases with patient-level data were included. Analysis of the reported cases in the literature demonstrates similar incidence of immune-related adverse events in patients with ESKD receiving dialysis as compared to the general population (49%). Grade 3 and 4 adverse events had been seen in fifteen patients (16%). Cancer remission (complete and partial) was seen in close to 30% of patients. Stable disease was seen in 28% and progression of disease in approximately 36% of patients. Of 66 cases the patients died. Urothelial and RCC represented approximately half of all treated cancers, and accounted for approximately 50% of all deaths reported. Eighteen of the reported dialysis patients had prior kidney transplant. Of these, 11 (61%) initiated dialysis after ICI-related rejection of their kidney allograft.

Conclusions: ICI is well tolerated in ESKD patients. Additional data in the dialysis population with use of ICI, and involvement in prospective studies, is needed to better assess outcomes, particularly within specific cancer types.
Methotrexate-Induced AKI: Incidence, Risk Factors, and Recovery

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Background: Data on short and long term renal outcomes after high dose methotrexate (HD MTX) in adult cohorts using a standard definition of AKI is lacking. This is a report on the incidence of AKI after HD MTX, renal outcomes when HD MTX is continued after AKI, and long term renal function in patients who survived beyond 5 years after Risk factors for AKI following HD MTX were also examined.

Methods: In this single center retrospective case control study, all adult patients (<18 years) who had received HD MTX (defined as 1g/m²) from 2003 – 2013 were analyzed. AKI was identified by a >1.5x increase in baseline serum creatinine (Cr) within 4 days after HD MTX. We have collected age at first HD MTX, race, cancer, baseline and all Cr values after HD MTX, and cumulative dose (CD) of MTX. Univariable and multivariable logistic regression models were performed with AKI as the dependent variables. Overall survival for patients that had received HD MTX was presented in a Kaplan-Meier analysis. Results: In a cohort of 865 patients, 32.1% developed AKI. Patients who developed AKI had a lower baseline Cr (0.7 ± 0.2 vs 0.9 ± 0.2; p<0.001), a higher eGFR (95.1 ± 21.8 vs 90.0 ± 22.0; p<0.001) and received a higher CD (25,750 (14100 – 35000) vs 20,000 (9425 – 34,300); p<0.01). There was no statistical difference in overall survival among patients who developed AKI (p=0.13) (Figure 1) and those who continued to receive HD MTX after AKI (p=0.32) (Figure 2). Recovery from AKI to within 20% of baseline Cr was associated with a higher probability of survival (p<0.001).

Conclusions: Despite its relatively common incidence in adult patients receiving HD MTX, AKI does not affect overall survival and should not be a barrier to further administration of chemotherapy.

PO1876

Cerebral Salt Wasting Caused by High-Dose Methotrexate

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Introduction: Severe acute hyponatremia is a rare complication of high-dose methotrexate (HDMTX) use.

Case Description: We present an interesting case of a 54 year-old man with relapsed diffuse large B-cell lymphoma with central nervous system (CNS) involvement who received a chemotherapy regimen including HDMTX. He received a single dose of 7.2 g of intravenous HDMTX. Baseline serum sodium (Na) was 140 mmol/L. Within 48 hours serum Na dropped to 120 mmol/L and patient developed mild headache and confusion. Laboratory evaluation revealed a urine Na 245 mmol/L, fractional excretion of sodium (FeNa) 2.5%, urine potassium 47 mmol/L and urine osmolality 561 mOsm/kg. Serum tests showed Na 120 mmol/L, chloride 81 mmol/L, osmolality 245 mosm/kg, uric acid 2.5 mg/dL, TSH 0.6 uIU/mL, cortisol level 15 microg/dL, creatinine 0.6 mg/dL and a low serum ADH level (<0.8 pg/mL). Rest of serum electrolytes were within normal limits. Patient was polyuric and soon became hypotensive and tachycardic. He was treated with a combination of 3% hypertonic saline and oral loop diuretics with subsequent improvement in symptoms, increase in serum sodium and reduced natriuresis.

Discussion: Sodium depletion and adrenal insufficiency were ruled out by normal adrenal function tests and a normal serum cortisol level. He did not receive any diuretics. The patient’s condition improved when he was given 3% NaCl (1L/h) for 3 hours and 1 hour of 0.9% NaCl. Sodium level rose to 132 mmol/L and he was discharged on outpatient basis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
POI1877

Cisplatin-Induced AKI Cancer Mouse Model Refinement
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Background: Cisplatin (CIS), a common chemotherapy agent, causes acute kidney injury (AKI) in up to one-third of patients. Traditional mouse models use healthy mice and a single, lethal dose of CIS (20-30 mg/kg). This model does not accurately reflect the clinical use of CIS where cancer patients receive 25-100 mg/m² every 3-4 weeks. There is a need for a multi-dose mouse cancer model of CIS-AKI that more closely reflects CIS clinical use.

Methods: C57BL/6 male mice (8 weeks old; n=45) were injected in the right flank with murine lung cancer cells (CMT167). 0.15×10⁶ cells were used. Subcutaneous solid tumors were allowed to grow for ~2 weeks until digital caliper measurement confirmed they were ≥50 mm³. Mice were then dosed with CIS (0, 12.5, 15 mg/kg) or vehicle (saline) 1x/week for up to 4 weeks. Mice were evaluated for outcomes of general health (body weight), survival, cancer progression (tumor volume), and kidney injury (Scr, BUN, KIM-1). Assessments were performed a 1x/week until sacrifice after 1-4 weeks of CIS treatment.

Results: Analyses for differences from baseline to sacrifice based on both cancer cells injected and CIS dose were assessed by 2-way ANOVA with a Tukey-Kramer post-hoc test, p<0.05 was considered statistically significant.

Results: Groups injected with ≥1 million CMT167 cells experienced the greatest decline in survival due to rapid tumor growth and ulceration (0% at 8 d). Cancer-free mice treated with CIS also experienced poor survival due to dehydration and weight loss (60% at 15 d). Mice injected with 50,000 CMT167 cells had the best survival (100% at 13 d). Body weight was significantly decreased as CIS dose increased (p=1.9×10⁻⁷) and increased as number of CMT167 cells increased (p=5.5×10⁻⁵). Tumor volume was significantly increased as number of CMT167 cells increased (p=5.1×10⁻⁶) and somewhat decreased as CIS dose increased (p=0.002). CIS dose did not significantly impact BUN or Scr levels but an increase in KIM-1 was somewhat associated with an increased CIS-AKI dose (p=0.105; 12.5 vs 15 mg/kg CIS p=0.191). There were no significant differences in body weight, tumor volume, or survival between the 12.5 and 15 mg/kg CIS treated mice.

Conclusions: The results indicate that the ideal CMT167 mouse cancer model of CIS-AKI should use 50,000 CMT167 cells and 15 mg/kg CIS. This model can be used to better understand CIS-AKI and to test potential protective compounds.

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POI1878

Renal Outcomes in High-Dose Cisplatin in Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A New and Interesting Perspective
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Background: Three-weekly high-dose cisplatin (100 mg/m⁲) concomitant to radiation therapy represents the standard of care with a curative intent in most of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Nevertheless, cisplatin is known as a particularly nephrotoxic drug especially at the cumulative dose of 200 mg/m² or more. Aim of this study was to investigate the incidence of AKI in patients with LA-SCCHN during and after treatment with high-dose cisplatin-based CRT to identify risk factors for cisplatin-induced AKI.

Methods: A consecutive cohort of 82 patients treated with cisplatin cumulative dose ≥200mg/m² concomitant to radiotherapy, was enrolled in a tertiary single Hospital between 2019 and 2020. Serum creatinine, hemoglobin, lymphocytes and eGFR formulas (CKD-EPI, MDRD, Cockcroft-Gault) were detected at baseline and after each cycle of chemotherapy. AKI and CKD onset were determined according to K-DIGO criteria. Clinical tumor stage as well as comorbidities were also included. Bayesian linear regression model was used to evaluate the impact of the clinical and pathological features on eGFR decay through cycles.

Results: At baseline, 57% of pts were CKD I stage, 37% CKD II stage, 6.1% CKD III stage A-B. Medium decay of eGFR from the baseline to the end of 3 cycle is reported in table 1 showing CKD different stages. The marked decay appears in day 10 during cycle 2 (Figure 1). Performing a Bayesian linear regression over cycles, hypertension showed a remarkable impact on the eGFR decay through the therapy over time (Figure 2). However, the AKI incidence was very low in all CKD classes; 2.4% in 1 cycle, 4.8% in 2 cycles and 8.5% in 3 cycle.

Conclusions: Surprisingly, from these data high dose of cisplatin seems feasible in different CKD stages with very low rate of renal toxicity events and AKI-CKD onset.

POI1879

Double Hit: A Case of Chromogranin A-Mediated Proximal Tubulopathy That Progressed to Full-Blown Fanconi Syndrome After Treatment with Everolimus
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Introduction: Hypophosphatemia is an independent risk factor for poor patient outcomes. We present a rare case of hypophosphatemia from a complication of a neuroendocrine tumor (NET) and the treatment for it.

Case Description: A 54-year-old female with metastatic NET presented with dyspnea. Patient had Pneumonia which was treated but a comprehensive electrolyte panel revealed profound hypophosphatemia (phosphorous levels < 1mg/dl). Initial suspicion was that poor nutritional status may be the underlying etiology, however despite aggressive intravenous phosphorus substitution the hypophosphatemia did not progress. Workup revealed obvious evidence of Fanconi syndrome. Patient had profound glucosuria with normal serum glucose. 24 hours urine phosphor excretion was markedly elevated at 900 mg. Vitamin D level was borderline low but activated (1,25-vitamin D levels) were markedly low at 1.8 pg/ml. PTH levels were only mildly elevated at 120 pg/ml. A deeper investigation into her course found that patient was diagnosed with a NET 8 months prior to this presentation and had evidence of mild glucosuria with mild-moderate hypophosphatemia at that time. Chromogranin A levels from her NET were substantially elevated at that time. Serial urine analyses during the course of her disease were reviewed, and it was evident that the glucosuria became markedly worse after the patient was started on everolimus therapy. We concluded that hypophosphatemia in this patient is from chromogranin A mediated proximal tubulopathy that developed to full blown Fanconi Syndrome after everolimus. We changed phosphorous supplementation to oral only and recommended holding everolimus provided it was appropriate from an oncological standpoint. Follow up of the patient in 4 weeks off everolimus showed continued improvement in phosphorous levels.

Discussion: Both chromogranin-A and mtor inhibitors have shown to cause acute tubular injury in proximal tubules. Our case is unique in the sense that it presented as severe hypophosphatemia from Fanconi syndrome secondary to two uncommon culprit agents that acted in a sequential manner to worsen the proximal tubulopathy. Based on this case we recommend that in NET patients with high chromogranin A levels, we check for signs of proximal tubulopathy before starting mtor inhibitor therapy.
Conclusions: Our study surprisingly highlights that both cisplatin/carboplatin-based CT and immunotherapy display a similar incidence of AKI and eGFR decay over time in NSCLC metastatic patients.

PO1881
AKI with BRAF and MEK Inhibitors May Not Be a Class Effect
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Introduction: BRAF tyrosine kinase inhibitors are used in the treatment of BRAF mutant metastatic melanoma. Simultaneous MEK inhibition has been shown to result in better response rates and fewer side effects. Renal toxicity has been reported with these agents which can include AIN, ATN, and Fanconi syndrome. We report a case of AKI due to biopsy proven AIN from BRAF and MEK inhibitor vemurafenib and cobimetinib.

Case Description: This is a 64-year-old woman with diabetes mellitus type 2, stage IV melanoma with BRAF V600E mutation and baseline serum creatinine (SCr) of 0.8 (0.6-1.1) mg/dL. She has been treated with multiple chemotherapy regimens and immunotherapy (last dose of immunotherapy 28 months prior to presentation). Patient received vemurafenib and trametinib until 8 months prior to presentation but stopped due to development of fever and AKI (SCr 1.7mg/dL). She was started on vemurafenib 480 mg BID every other day and cobimetinib 40mg every other day 6½ months before presentation. Two months later the vemurafenib dose was increased to 960mg BID but was noted to have AKI with SCr of 4.5 mg/dL and vemurafenib and cobimetinib were stopped. Her blood pressure was elevated to 154/70 mmHg. Urinalysis showed protein of 100 mg/dL, 0-3 RBC/HPF and 0-6 WBC/HPF. SCr improved to 2.2 mg/dL but remained elevated and renal consult was obtained with subsequent kidney biopsy. It showed active, subacute, and chronic interstitial nephritis with extensive tubular atrophy. Patient was treated with prednisone 50 mg daily and was tapered down to 10 mg daily over two months. Repeat CT scan showed new perinephric nodules and she was started on a new BRAF/MEK combination of encorafenib and binimetinib. She is currently tolerating these medications with SCr stable at 1.5mg/dL.

Discussion: BRAF and MEK inhibitors are associated with AKI secondary to ATN and AIN. In the above case, the patient developed AIN with vemurafenib and cobimetinib which were discontinued resulting in significant improvement in kidney function. Due to progression of disease she was started on encorafenib and binimetinib which she is currently tolerating well. This case demonstrates that renal toxicity from BRAF and MEK inhibitor may not be a class effect and may also be dose dependent. It may be possible to consider a dose reduction or switch to another medication in the same class if renal toxicity is noted.

PO1882
Acute Proteinuric Renal Failure in a Lung Cancer Patient Treated with Poziotinib: First Case Described in the Literature
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Introduction: The therapeutic approach to non-small cell lung cancer (NSCLC) has changed significantly in recent years: genomic drivers have enabled the development of new molecularly targeted therapies. The improvements obtained in the survival of these patients, the adverse events related to these novel treatments should not be forgotten. Poziotinib is a new generation tyrosine kinase inhibitor which has been recently registered for the treatment of patients with EGFR/HER2 exon 20 insertion mutations.

Case Description: In 2017, a 58-year-old woman was diagnosed with a pt2, N2, M0, G2 NSCLC for which she was surgically treated with lobectomy and lymphadenectomy, followed by adjuvant CT, and after metastatic relapse, further CT until July 2020. Upon progression, she started Poziotinib. She was referred to us due to the occurrence of hyperglycemia, hypokalemia and proteinuria (2.8 g/24 h), despite a normal renal function,. The objective examination and blood tests were all normal, and the patient did not report any symptom. Due to a quick worsening of renal function (SCr 2 mg/dL), and in particular of proteinuria (3.3 g/24 h), Poziotinib was stopped and dexamethasone 4 mg/day was started. Examinations for glomerulopathies were not diriment, a renal biopsy was performed in order to guide therapeutic decisions. The histological picture showed incomplete glomerular sclerosis (5/15 glomeruli), outbreaks of tubulointerstitial sclero-atrophy, as well as interstitial inflammatory lymphoplasmacytic infiltrate; immunohistochemistry was negative for all antinuers, while electron microscopy is presently still in progress. Following the discontinuation of Poziotinib, a progressive improvement of AKI and a reduction of proteinuria (1.3 g/24 h) was observed, allowing to hold the drug accountable, in the absence of any other risk factor, for the renal AE observed. From a histological viewpoint, nephroangiosclerosis was documented, while dialysis therapy may have hidden peculiar glomerular lesions. Poziotinib wasn’t resumed.

Discussion: This is the very first case of renal toxicity from Poziotinib treatment reported so far. Cases like this highlight the need for both a nephro- oncological evaluation as well as for dedicated paths to perform rapid renal biopsies in order to characterize these events and improve their management.

PO1883
Enfortumab Vedotin-Induced Diabetic Ketoacidosis and AKI: A Case Report
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Introduction: Enfortumab vedotin is a novel antineoplastic agent in the management of advanced urothelial cancers. While hyperglycemia has been reported, diabetic ketoacidosis and AKI are rare.

Case Description: A 69-year-old man with history of metastatic urothelial cancer (treated with carboplatin/gemcitabine and Nivolumab) and CKD who presented to hospital one week after receiving Enfortumab with Diabetic Ketoacidosis (DKA) and AKI with Cr of 3.6mg/dL (Baseline 1.8mg/dL). Urine microscopy revealed granular casts consistent with tubular injury. Patient remained hyperglycemic despite titrating dose of IV regular insulin and subsequently developed shock, toxic epidermal necrolysis, and worsening renal failure with anuria requiring continuous renal replacement therapy. Despite maximal support, patient passed away.

Discussion: Enfortumab vedotin comprises antinectin-4 antibody and a microtubule-disrupting agent monomethyl auristatin E (MMAE). The drug binds to Nectin-4, expressed on tumor cells, with high affinity, which induces the internalization of MMAE and leads to subsequent cell apoptosis through impaired cell division. Dermatologic toxicity occurs from drug binding to Nectin-4 expressed on normal skin cells. AKI was reported in 1% of patients of the phase 2 trial but not in the phase 3 trial. Nectin-4 protein expression is known to be stained in renal tubular epithelial cells. While DKA may have contributed to our patient’s tubular injury, direct tubular toxicity may be possible and requires further research. Physicians prescribing Enfortumab vedotin should be aware of this potential side effect.
reported an increase in serum creatinine. In our case, the difference between eGFR by cystatin C and by serum creatinine demonstrated not a true decrease in kidney function. We have attributed these events to inhibition of the tubular secretion of creatinine by palbociclib and decided to continue treatment with palbociclib. Physicians should be aware that patients undergoing therapy with palbociclib require monitoring of kidney function and an increase in serum creatinine from baseline, might represent an inhibitory effect of the secretion of creatinine and not an actual decrease in kidney function.

**PO1885**

A Case of IgA Nephropathy in the Setting of Sezary Syndrome and Mogamulizumab

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**Introduction:** IgA Nephropathy (IgAN) is an autoimmune disease with complex pathogenesis. Sezary syndrome (SS) is a leukemic subtype of cutaneous T cell lymphoma (CTCL). A rare association has previously been reported between IgAN and CTCL. Mogamulizumab (MG) is a monoclonal antibody drug targeting C-C chemokine receptor type 4 (CCR4) and is used in the treatment of CTCL and SS. MG has been associated with drug eruptions and systemic immune-mediated adverse events.

**Case Description:** A 63 year-old woman with SS was treated with MG. Her skin symptoms improved and circulating Sezary cells cleared. Due to a cutaneous drug eruption, the frequency of MG administration was reduced to monthly after cycle 7. Labs prior to cycle 19 demonstrated serum creatinine (Cr) 1.77 mg/dL from a prior baseline ~0.9-1.0 mg/dL. She received intravenous fluids but Cr worsened to 3.97 mg/dL. Urinalysis (UA) revealed more than 20 red blood cells (RBCs) per high powered field (HPF). 24 hour urine protein to creatinine ratio (UPCR) was 2.03 g/g. Serum creatinine (Cr) was increased to 1 mg/kg/day and tapered over 6 months. MG was stopped. After 6 months Cr had improved to 1.10 mg/dL. UA showed 3-5 RBCs per HPF with UPCR of 0.122 g/g. Her SS remained well controlled without systemic therapy.

**Discussion:** This case reinforces the association between IgAN and CTCL which has been described in prior case series. In patients with CTCL, altered T cell populations and a dysregulated immune response may contribute to the pathogenesis of IgAN. Complicating this is the use of MG which can deplete normal CCR4-expressing regulatory T cells by inducing antibody-dependent cellular cytotoxicity. MG is associated with cutaneous granulomatous drug eruptions in which alterations in T cell populations have been implicated. Systemic autoimmune complications outside of the kidneys have also been reported. The possibility that MG could play a role in IgAN should be considered.

**PO1886**

Filgrastim-Induced Crescentic Glomerulonephritis

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**Introduction:** Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is caused by deposition of monoclonal immunoglobulins in the glomeruli. It is one of renal disorders included in the spectrum of monoclonal gammopathy of renal significance (MGRS). IgG3 with kappa light chain is the most common type. Autologous stem cell transplantation (SCT) provides a durable remission and better renal outcomes. Granulocyte colony stimulating factor (GCSF) is a recombinant glycoprotein used for mobilization of bone marrow in SCT. GCSF has been implicated as a cause of crescentic transformation of an acute glomerulonephritis in one prior case with a monoclonal deposits in a kidney transplant patient. In this case, we report the clinical and pathologic findings of GCSF induced exacerbation and crescentic transformation of pre-existing PGNMID with successful treatment and SCT.

**Case Description:** A 48-year-old male with recent diagnosis of MGRS presenting as MPGN and monoclonal IgG Kappa with C3 deposits on biopsy and treated with Velcade, cyclophosphamide and dexamethasone with a plan for SCT. Patient was admitted after acute increase in creatinine from 2.87 mg/dL to 6.69 mg/dL with hematuria and proteinuria after receiving GCSF during stem cell mobilization. Timing of acute renal injury correlated with increase in WBC after GCSF injections with a peak of 69 K/ul. Repeat biopsy kidney biopsy was significant for crescentic membranoproliferative (62% crescents) glomerulonephritis with monoclonal IgG Kappa deposits. Patient received 5 sessions of plasmapheresis, one dose of renally adjusted IV Cytospan, and pulse steroids followed with a taper. After a month he undergoes an Autologous SCT (creatinine at baseline 1.69 mg/dL). His kidney function continued to improve and after 16 months post SCT his creatinine is at 1.4 mg/dL.

**Discussion:** GCSF enhances neutrophils activation in large counts and induces its endothelial activation. In the presence of pre-existing renal pathology, MGRS and MPGN with IgG kappa and C3 deposits in this case, the localized immunoglobulin and complement deposits in the glomeruli can attract activated neutrophils leading to its infiltration and degranulation in the glomerular microenvironment, and resulting in rupture of glomeruli basement membrane and formation of crescent. Therefore, GCSF induced kidney injury should be suspected due to its potential risk for exacerbating pre-existing glomerulonephritis.

**PO1887**

Creatinine-Cystatin C Ratio and Mortality in Cancer Patients: A Retrospective Cohort Study

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**Background:** Muscle wasting is prevalent in cancer patients, and early recognition of this phenomenon is important for risk stratification. Recent studies have suggested that the creatinine-cystatin C ratio may correlate with muscle mass in several patient populations. The association between creatinine-cystatin C ratio and survival was assessed in cancer patients.

**Methods:** A total of 3,060 patients who were evaluated for serum creatinine and cystatin C levels at the time of cancer diagnosis were included. The primary outcome was 6-month mortality. The 1-year mortality, and length of intensive care unit (ICU) and hospital stay were also evaluated.

**Results:** The mean age was 61.6±13.5 years, and 1,409 patients (46.0%) were female. The median creatinine and cystatin C levels were 0.9 (interquartile range [IQR], 0.6-1.3) mg/dL and 1.0 (IQR, 0.8-1.5) mg/L, respectively, with a creatinine-cystatin C ratio range of 0.12-12.54. In the multivariate Cox analysis, an increase in the creatinine-cystatin C ratio was associated with a significant decrease in the 6-month mortality (per 1 creatinine-cystatin C ratio, hazard ratio [HR] 0.35; 95% confidence interval [CI], 0.28-0.44). When stratified into quartiles, the risk of 6-month mortality was significantly lower in the highest quartile (HR 0.30; 95% CI, 0.24-0.37) than in the lowest quartile. Analysis of 1-year mortality outcomes revealed similar findings. The highest quartile was also associated with shorter length of ICU and hospital stay (both P<0.001). These associations were independent of confounding factors.

**Conclusions:** The creatinine-cystatin C ratio at the time of cancer diagnosis significantly associates with survival and hospitalization in cancer patients.

**PO1888**

Comparison of Kidney Volume-Based Methodology to Glomerular Filtration Rate Estimating Equations to Predict Measured Glomerular Filtration Rate in Cancer Patients

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**Background:** Total kidney volume (TKV) has been associated with both measured glomerular filtration rate (eGFR) and with equations recommended to estimate GFR (eGFR) in clinical practice. However, there is scarce data comparing measurement of TKV to eGFR equations as predictors of eGFR, particularly in the oncology setting.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We enrolled 181 cancer patients treated at an academic tertiary cancer hospital in Brazil (Instituto do Cancer do Estado de Sao Paulo), who had undergone abdominal imaging and measurement of GFR by plasma clearance of 51Cr-EDTA within 60 days. eGFR was determined based on the CKD-EPI equation using Scr (eGFR-cre) and Scr combined with 24hrs Scr (eGFR-cre-cys). eGFR and mGFR were non indexed for body surface area. Total kidney volume (TKV) was measured using a semi-automatic segmentation program, excluding non-functional tissues. The correlations between mGFR and TKV as well as mGFR and eGFR were calculated using the Pearson correlation coefficient. Linear regression models for mGFR having TKV and eGFR equations as predictors were built.

Results: Patients were 55 (14.0) y, 50.3% male. Most common cancer sites were breast (22.7%), male genital (21.8%) and gastrointestinal (20.9%). ECOG levels 0/1 corresponded to 95% of patients. Mean (SD) Body mass index was 27.18 (5.18). Mean (SD) eGFR-cre and eGFR-cre-cys were 84.8(27.23), 90.4 (24.9), and 83.8 (25.9), ml/min, respectively. Mean (SD) TKV for both kidneys was 302.2 (77.9) cm3. PCC for mGFR-TKV, mGFR-eGFRcre and mGFR-eGFRcre-cys were 0.76, 0.78 and 0.85, respectively. TKV improved the coefficient of determination of the linear regression models when added to both eGFRcre and eGFRcre-cys, in overall and assessed subgroups (Table 1).

Conclusions: In conclusion, our results suggest that measurement of TKV is a reliable predictor of mGFR in cancer patients with the potential to be incorporated to the current eGFR equations used in clinical practice.

Table 1: Linear regression models for measured glomerular filtration rate.
Methods: We conducted a retrospective study in a tertiary referral center. We defined the clinical deterioration within two days following rituximab administration, including onset of new organ involvement or worsening of the underlying CV not clearly explained by disease progression alone - with or without laboratory evidence.

Results: Among 64 patients with known CV who received rituximab therapy in our center, 14 (22%) developed disease flare. Median age was 67.5 years. Seven patients (50%) had type II CV while the other half had either type I (n=6) or type III (n=1). Twelve patients (86%) had IgM-mediated CV flare. Twelve patients (86%) had an underlying B-cell lymphoproliferative disorder as the cause of their CV. CV flare occurred after a median time of 5.5 days (range: 2-8 days). The organ systems most involved were the skin (n=10), kidneys (n=5), and peripheral nerves (n=3). Nearly all patients received treatment directed against their underlying diseases, including chemotherapy, corticosteroids, and/or immunosuppressants. Patients who developed flares were more likely to have a B-cell lymphoproliferative disorder as the underlying etiology of their CV (p=0.03), had lower creatinine levels prior to rituximab treatment (0.8 vs. 1.05 mg/dL, p=0.01), and eventually received more treatments with plasmapheresis together with rituximab (p=0.03). Eight patients (77%) died after a median time of 27 months.

Conclusions: In our study, the prevalence of rituximab-associated flare of CV is 22%, and it can occur in all types of CV. Flares tend to arise about two days (less than one week) after rituximab administration and are more likely to happen in patients with an underlying B-cell lymphoproliferative disorder. These flares do not indicate failure of response to treatment. Clinicians should be cognizant of its existence and have a high index of suspicion for this phenomenon.

PO1892
Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits
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Introduction: Membranous-like glomerulopathy with masked monoclonal IgG deposits (MMGID) is a recently described entity characterized by a membranous pattern of injury with monoclonal IgG-kappa restriction, unmasked by plasmapheresis on formalin-fixed paraffin-embedded (FFPE) tissue by immunofluorescence microscopy (IF). Retrospective pathology and chart review was performed within a large health system in the USA between 2019-2021 identifying 5 patients.

Case Description: All 5 patients were Caucasian females with median age 17 years (range: 12-40). On presentation, 4 patients had elevated urine protein to creatinine ratio (UPC), 3 had microscopic hematuria, and 1 patient had an eGFR <90ml/min/1.73m². Retrospective pathology and chart review was performed within a large health system in the USA between 2019-2021 identifying 5 patients.

Conclusions: PO1893
Thrombotic Microangiopathy, Its Clinical Characteristics, Etiologies, and Outcomes: A Case Series of 33 Patients
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Background: Thrombotic Microangiopathy (TMA), is a pathologic pattern of injury that has a variable presentation and etiologies. Here we present a case series of 33 patients from our academic center with biopsy proven TMA, describe their clinical characteristics and compare the differences between drug-induced TMA and other causes of TMA (Table 1).

Methods: We collected data on clinical characteristics, detailed biopsy findings, etiologies and treatment details for 33 patients at our institution with biopsy proven diagnosis of TMA

PO1894
TAFRO: A New Cause for Thrombotic Microangiopathies Mimicking Atypical Hemolytic Uremic Syndrome Successfully Treated with Anakinra and Eculizumab

Introduction: AtTAFRO is syndrome of Castelmann’s disease with: thrombocytopenia, anasarca, myelofibrosis, AKI & organomegaly. We present a 17 yr old girl with abdominal lymph nodes who rapidly developed anasarca, splenomegaly, AKI requiring dialysis, anasarca, myelofibrosis, AKI & organomegaly. We present a 17 yr old girl with abdominal lymph nodes who rapidly developed anasarca, splenomegaly, AKI requiring dialysis, & respiratory failure requiring mechanical ventilation. After a lymph node bx 2 months later showed multicentric Castlemans’s, plasma cell variant, we realized she early on had TAFRO.

Case Description: She rapidly developed anasarca, an 18 cm spleen, & abdominal nodes to 1.9 cm. Bacterial cultures, spinal tap, viral resp panel, monon, HIV, HIV-8 levels were normal (NL). Hbg dropped to 6.7 g/dL without hemolysis, platelets 57,000 & WBC,15,500. CRP was 32.5 & sed rate 130. Oliguria ensued & creatinine rose to 3.6 mg/dl. Urinalysis had +1 protein, +3 blood with granular casts. ANA, ASO, streptozyme, myeloperoxidae, proetinase -3, serum immunofixation, anti-phospholipid antibody (ANA) in 1 patient (see table) who had a known history of juvenile idiopathic arthritis. Kidney biopsy revealed a membranous pattern of glomerular injury in all patients, with global glomerulosclerosis from 0-31%, segmental glomerulosclerosis from 2-7%, and interstitial fibrosis and tubular atrophy from 2-50%. Electron microscopy revealed subepithelial/intramembranous deposits without substructural organization. Finely granular capillary wall reactivity for C3 was noted on routine IF on frozen sections. On FFPE after plasmapheresis, all cases revealed glomerular capillary wall staining for gamma-1 (4 cases) or gamma-3 (1 case) and kappa light chains; lambda light chains were negative. Extensive hematologic workup was negative for monoclonal bands or lymphoproliferative processes. All patients were treated with angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy, and 2 patients were also treated with Rituximab. Four patients had an improvement in UPC. None of the patients required kidney replacement therapy.

Discussion: MGMD is a peculiar entity with monoclonal IgG glomerular deposits primarily affecting young Caucasian females, without obvious correlation to monoclonal lymphoproliferative disorder. Treatment with ACEi or ARB +/- Rituximab improved UPC in most patients in this case series. Better understanding of this entity is important to guide therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Large Abdominal Mass: An Unusual Presentation of Multiple Myeloma
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Introduction: Extramedullary Soft Tissue Mass (ESTM) is an infrequent presentation of Multiple Myeloma. We present a unique case of Multiple Myeloma with very large bulky tumor masses.

Case Description: A 69 year old AA female presented with severe abdominal distention. CT Scan showed a 17 x 10 x 10 cm mass originating in the retroperitoneal region, a 12.5 cm mass in the pelvis and a 4.3 x 2.7 cm mass in the liver as shown in the image. Further testing showed anemia and renal failure. Biopsy of the mass revealed multiple myeloma, driving a monoclonal IgG lambda clone. FISH panel was positive for 17p/13p deletion which is very unfavorable. Patient was treated initially with dexamethasone/cyclophosphamide/Velcade and later with Daratumumab/Carfilzomib/dexamethasone without any response and remained on dialysis ultimately succumbing within 6 weeks of diagnosis.

Discussion: Initial Extramedullary Soft Tissue Mass (ESTM) manifestations in Multiple Myeloma occur in about 3% of the cases. In a large majority (93.5%) these lesions are solitary. Our patient had large, multiple masses with high tumor burden and unfavorable cytogenic signature. She did not respond to therapy despite utilization of aggressive regimens. This is a very unique presentation of myeloma and with the unfavorable characteristics, had a dismal prognosis despite aggressive therapy.

Fibrils in mesangial matrix
DNAJB9 staining

PO1896
Fibrillary Glomerulonephritis and Graft vs. Host Disease
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Introduction: Fibrillary Glomerulonephritis (FGN) is rare and seen in 1% of kidney biopsies. Etiology is unknown. It is associated with malignancy, monoclonal gammopathy, autoimmune disorders and infections. There has not been FGN case reported in a pt with Graft Versus Host Disease (GVHD). We present a case AKI see to FGN with h/o Acute Lymphocytic Leukemia, status post Allogeneic Stem Cell Transplant complicated by Gastrointestinal GVHD.

Case Description: 67 yo African American female with DM, HTN, ALL s/p ASCT in remission, recently diagnosed with GI GVHD, presented with nausea, vomiting & diarrhea. Vitals: BP 140/70, Temp 37.4°C, HR 109. Exam showed 3+ LEs edema. Labs: Cr 3.5 mg/dL, baseline of 1.1mg/dL. Urinalysis showed hematuria and 14.6g/g protein. Histology showed C3 crescentic GN. DNAJB9 stain returned positive and EM findings confirmed FGN. Patient received Soulmeth, followed by Rituximab and then Cyclophosphamide. She was dialysis dependent within 6 mos of diagnosis.

Discussion: FGN may have an undescribed association with GVHD. It is understudied because of rarity. It can present with AKI and kidney bx is needed for diagnosis and to guide treatment. The trigger to get biopsy was the unexplained protein & blood in urine. Ct stabilized initially. However, earlier diagnosis and treatment could have delayed progression to ESRD.

PO1897
Recurrent Fibrillary Glomerulonephritis Secondary to Chronic Lymphocytic Leukemia: A Rare Case of Treatment Success
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Introduction: Fibrillary GN is a rare form of glomerular disease characterized by the random deposition of small (20nm) fibrils in the mesangium and capillary walls of the glomerulus. There is a recognized association with hepatitis C, malignancy and autoimmune conditions. It is poorly responsive to treatment and up to half of the patients reach ESRD by six years. We present a case of Fibrillary GN secondary to CLL with complete remission after receiving Bendamustine and Rituximab and a subsequent relapse treated with ibrutinib with good renal recovery.

Case Description: A 69-year-old male presented in 2014 with a pathological spinal fracture and was subsequently found to have CLL. He had normal renal function and no proteinuria at the time of diagnosis and his CLL was managed conservatively. In 2016 he developed nephrotic syndrome (ACR >1000) with a significant decline in renal function of injury with fibrils on electron microscopy suggesting fibrillary glomerulonephritis. He received Bendamustine and Rituximab for CLL and went into complete remission of his nephrotic syndrome and improvement in renal function to eGFR of 57ml/min.
He remained in remission for four years. In 2020 he had relapse of his nephrotic syndrome and eGFR dropped to 17ml/min. Further imaging suggested progressive disease of the kidney. He had a further renal biopsy which again confirmed recurrent Fibrillar GN. He was started on the Tyrosine kinase inhibitor (TKI) Ibrutinib in December 2020 and within 3 months his renal function had improved to an eGFR of 33ml/min and reduction in proteinuria.  

TKIs have mostly been linked with kidney injury secondary to the potential deleterious effects on the renal endothelium. This is the first reported case of the use of a TKI as a treatment for Fibrillar GN secondary to CLL. In addition, there is scarcity of experience with relapse of Fibrillar GN as it usually a progressive disease and with little prospect of recovery. This case highlights the following: If there is an identifiable cause driving Fibrillar GN, treatment can be associated with remission of proteinuria and improvement in renal function. Monitoring of the underlying disease is important as recurrence can result in subsequent relapse of nephrotic syndrome. TKIs used with caution can be beneficial in the setting of MGRS.

PO1898
Ruxolitinib for Graft vs. Host Disease-Associated Nephrotic Syndrome: A Case Report

Introduction: Graft-versus-host disease (GVHD) is a serious complication of allogeneic stem cell transplant in which donor T-cells attack the host antigens. We report a case in which ruxolitinib successfully treated GVHD-related nephrotic syndrome.

Case Description: A 48-years-old male known to have myelodysplastic syndrome (MDS) was referred for evaluation of proteinuria. He was diagnosed with MDS four years ago. This disease was persistent with azacitidine. He received an allogeneic stem cell transplant (SCT) about a year after the MDS diagnosis and he achieved complete remission. However, the post-transplant course was complicated by chronic GVHD which manifested mainly as non-specific interstitial pneumonia (NSIP) about three and a half-year post-transplant. NSIP was treated with high-dose oral steroid therapy, which was down to a maintenance dose of 10 mg daily, and Mycophenolate Mofetil. During his course of GVHD, he had persistent mild proteinuria (UPCR less than 1 g/g of creatinine) without active urine sediment. This proteinuria was noted initially prior to NSIP diagnosis, improved while on high-dose prednisone but progressively worsened after the prednisone was tapered to 10 mg once daily. The proteinuria peaked at 2.4 g/g of creatinine with hyperalbuninemia of 2.6 g/dl at which point it was investigated with a renal biopsy. Renal biopsy showed Membranous Nephropathy with negative staining for anti-PLA2R antibody. The patient was started on ruxolitinib at a dose of 10 mg twice a day. Subsequent follow-up showed dramatic reduction in proteinuria. UPCR (g/g of creatinine) of 0.96, 0.4 and 0.09 was noted at 1, 2- and 5-months post-therapy initiation respectively.

Discussion: Nephrotic syndrome is a rare manifestation of GVHD with membrane nephropathy histology seen in almost two thirds of patients. Traditionally treated with high-dose steroid with variable efficacy, we decided against it due to the patient-reported adverse effects from prior high-dose steroid therapy. Recent studies such as REACH2 and REACH3 trials have demonstrated that ruxolitinib, a selective Janus Kinase (JAK) 1 and 2 inhibitor, has superior efficacy than other second-line therapy options available. Hence, ruxolitinib can be considered in GVHD-associated nephrotic syndrome especially if a steroid-sparing approach is needed.

PO1899
Clonal Hematopoesis of Indeterminate Potential Is Associated With Worse Kidney Function and Anemia in a Cohort of Patients with Advanced CKD
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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an inflammatory premalignant disorder resulting from acquired genetic mutations in hematopoietic stem cells. CHIP is common in aging populations and associated with cardiovascular morbidity and overall mortality, but its role in chronic kidney disease (CKD) has not been investigated.

Methods: We performed targeted sequencing to detect CHIP mutations in a cohort of 87 adults with advanced CKD (eGFR < 60 ml/min/1.73m2). Kidney function, hematologic, and mineral bone disease parameters were assessed cross-sectionally at baseline, and a total of 2,091 creatinine measurements and 3,382 hemoglobin measurements were retrospectively collected over the following 12-year period.

Results: At baseline, 20 of 87 (23%) cohort participants had CHIP detected. Those with CHIP had lower baseline eGFR (22.3 ± 2.5 vs. 28.2 ± 1.4 ml/min/1.73 m2, P = 0.04) in age-sex-and-adjusted regression models. Individuals with CHIP had a 2.5-fold increased risk of a 50% decline in eGFR or eSKD in a Cox proportional hazard model adjusted for age and sex (95% confidence interval, 1.3–4.7). Further, those with CHIP had lower hemoglobin at baseline (11.6 ± 0.3 vs. 12.8 ± 0.2 g/dL, P = 0.0003) and throughout the follow-up period despite a greater use of erythropoiesis-stimulating agents. Mean cell volume was associated with variant allele fraction, suggesting CHIP may contribute to defective erythropoiesis in CKD.

Conclusions: CHIP was associated with lower eGFR, progression of CKD, and anemia in individuals with advanced CKD. Further assessment of the direction of causality between CHIP and CKD and validation in additional cohorts is required.

Funding: Private Foundation Support

PO1900
Case of C3 Glomerulopathy in a Patient with Mesotheiloma

Introduction: C3 glomerulopathy has been described in autoimmune diseases and in monoclonal gammapathy caused by plasma cells and B-cell lineage cell malignancies. There have been no reports of C3 glomerulopathy that is associated with mesothelioma. We report here a case of C3 glomerulonephritis was diagnosed in patient with pulmonary mesothelioma.

Case Description: 84-year-old male patient presented with shortness of breath with fluid overload and vasculitic rash in the lower extremities, elevated BUN and creatinine and potassium of 5.7. Patient has been diagnosed with resectable pulmonary mesothelioma two months prior to his presentation and had received only one treatment of immune check inhibitor (Nivolumab plus Ipilimumab) one day prior to admission. Work up was done and showed AKI, proteinuria and hematuria, but negative work up for autoimmune disease or paraproteinemia or an infectious etiology. Decision was made to proceed with kidney biopsy which showed C3-dominant immune-complex mediated glomerulonephritis affecting about 35% of glomeruli with segmental crescent formation in about 5% of the glomeruli, diffuse acute tubular injury and minimal interstitial fibrosis and tubular atrophy.

Discussion: C3 glomerulopathy has been associated with autoimmune diseases and hematological malignancies and is related to uncontrolled activation of the alternative complement pathway, however solid tumors like mesothelioma may also trigger an immune mechanism that would lead to C3 glomerulopathy. We will discuss the possibility that the C3 glomerulopathy was due to or in association with the recent diagnosis of mesothelioma, also we will discuss the possible mechanisms of this association.

PO1901
NELL-1 Membranous Nephropathy Associated with Diffuse Reactive Lymphadenopathy
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Introduction: We present a case of a neoplastic epidermal growth factor like-1 (NELL-1) MN associated with diffuse lymphadenopathy without evidence of malignancy or autoimmune disease.

Case Description: A 53-year-old woman with a BRCA 1 mutation presented with nephrotic syndrome. Diffuse lymphoproliferative disorder was found on examination. Laboratory evaluation revealed serum albumin of 1.9 mg/dl, creatinine of 0.4 mg/dl, and UPCR 13.5 g/g. Urine microscopy showed protein (4+), and bland urine sediment. Serum PLA2R antibody was negative. Four excisional lymph node biopsies were performed, all of which revealed reactive hyperplasia without evidence of hematological malignancy. Flow cytometry and a bone marrow biopsy were negative. Serology for ANA, CRP, ESR, C3, C4, EBV, HIV, and Hepatitis B, C were all negative. Renal pathology revealed diffuse, fine pinholes along the glomerular basement membranes using a Jones silver stain. Immunohistochemistry for autoimmune disease or paraproteinemia or an infectious etiology. Decision was made to proceed with kidney biopsy which showed C3-dominant immune-complex mediated glomerulonephritis affecting about 35% of glomeruli with segmental crescent formation in about 5% of the glomeruli, diffuse acute tubular injury and minimal interstitial fibrosis and tubular atrophy.

Discussion: C3 glomerulopathy has been associated with autoimmune diseases and hematological malignancies and is related to uncontrolled activation of the alternative complement pathway, however solid tumors like mesothelioma may also trigger an immune mechanism that would lead to C3 glomerulopathy. We will discuss the possibility that the C3 glomerulopathy was due to or in association with the recent diagnosis of mesothelioma, also we will discuss the possible mechanisms of this association.
Results: Through real-time PCR, western blot and masson staining, successful establishment of a mouse model with cisplatin induced renal interstitial fibrosis was confirmed. Through RNA high-throughput sequencing, 387 long noncoding RNAs (lincRNAs) and 2427 mRNAs were differently expressed between cisplatin group and control group. The expression of IncRNA MSTRG.8677 and IncRNA MSTRG.405 were verified by real-time PC with the same tendency as RNA sequencing. Complement C3 was found to be at the top among the different expressed mRNAs by RNA sequencing. Several terms related to immunity were found to be within the top 20 terms through GO enrichment analysis of different expressed mRNAs. Systemic lupus erythematosus pathway (ko5322, Q=3.4e-17), including the complement cascade pathway, was found to be the top pathway through KEGG enrichment analysis of different expressed mRNAs. The mRNA expression of C3, C1q, C2 and C4 were found to upregulated remarkably in cisplatin group by RNA sequencing and verified by real-time PCR.

Conclusions: Renal interstitial fibrosis could be induced by intraperitoneal injection of cisplatin periodically in mice, with complement cascade pathway activation in the diseased kidney.

Funding: Other NIH Support - National Natural Science Foundation of China (No.81800595)

PO1903

Complement Activation in a Mouse Model of Cisplatin-Induced Renal Interstitial Fibrosis

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Background: Cisplatin is widely used for tumor chemotherapy. Renal interstitial fibrosis and chronic renal failure could be induced by periodic use of cisplatin. The mechanism of cisplatin induced renal interstitial fibrosis needs to be clarified.

Methods: In cisplatin group, male C57BL/6 mice were intraperitoneally injected with cisplatin (10mg/kg) on day 0, 7 and 21, and killed on day 28. In control group, mice were intraperitoneally injected with saline and killed at the same timepoint as cisplatin group. The kidney tissue was collected for RNA Illumina high-throughput sequencing, real-time PCR, western blot and masson staining.

Results: Through real-time PCR, western blot and masson staining, successful establishment of a mouse model with cisplatin induced renal interstitial fibrosis was confirmed. Through RNA high-throughput sequencing, 387 long noncoding RNAs (lincRNAs) and 2427 mRNAs were differently expressed between cisplatin group and control group. The expression of IncRNA MSTRG.8677 and IncRNA MSTRG.405 were verified by real-time PC with the same tendency as RNA sequencing. Complement C3 was found to be at the top among the different expressed mRNAs by RNA sequencing. Several terms related to immunity were found to be within the top 20 terms through GO enrichment analysis of different expressed mRNAs. Systemic lupus erythematosus pathway (ko5322, Q=3.4e-17), including the complement cascade pathway, was found to be the top pathway through KEGG enrichment analysis of different expressed mRNAs. The mRNA expression of C3, C1q, C2 and C4 were found to upregulated remarkably in cisplatin group by RNA sequencing and verified by real-time PCR.

Conclusions: Renal interstitial fibrosis could be induced by intraperitoneal injection of cisplatin periodically in mice, with complement cascade pathway activation in the diseased kidney.

Funding: Other NIH Support - National Natural Science Foundation of China (No.81800595)
cycle and at the same time plasma and urine were collected. Klothe plasma levels were measured in 4 phases diagnosis (t1); onset of AKI/2 months from diagnosis in patients without damage (t2); 15 days after t2 (t3); bone marrow tx (t4)

**Results:** We measured Klothe levels in 13 patients. The subjects are respectively 9 M and 4 F, mean age 49 years, all with normal renal function (mean creatinine 0.81 mg/dL) at diagnosis. The mean number of chemotherapy courses was 3.2. 7 patients developed stage 1 AKI according to AKIN criteria. No differences in anthropometric parameters were observed between the two groups. In subjects with development of renal damage, the average time of development was 2 months from diagnosis. While plasma Klothe decreases in a similar way in the first CT in the two groups, in no-AKI group the filtrate return normal before the next cycle. The restoration of normal kidney function is not observed in the AKI group (MANOVA p > 0.006)

**Conclusions:** This trend allows us to hypothesize that Kl is an indication of incomplete recovery of renal (tubular?) function before the next CT cycle, predisposing to the development of kidney disease

**Funding:** Private Foundation Support

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**PO1905**

Systemic Amyloidosis Presenting as Progressive Dysphagia, Hypercalcemia, and Proteinuria

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**Introduction:** Systemic amyloidosis consists of several disorders whereby amyloid fibrils deposit in the extracellular tissue of multiple organs and as such, is associated with a wide spectrum of disease leading to significant morbidity and mortality. The severity and clinical manifestations of systemic amyloidosis is highly dependent on the site of amyloid fibril deposition.

**Case Description:** We present a 75-year-old male with no medical history who presented with dysphagia and epigastric abdominal pain. Lab work revealed moderate hypercalcemia and acute kidney injury (AKI) with urinalysis significant for >500mg/dL of protein. He received intravenous fluid resuscitation with improvement in renal function and temporary resolution of hypercalcemia. His AKI and hypercalcemia were attributed to volume depletion and possible milk-alaki syndrome due to consumption of calcium carbonate. After discharge however, he continued to have persistent sub-nephrotic range proteinuria, mild hypercalcemia and progressive renal insufficiency. UPEP and serum free light chain analysis revealed elevated kappa light chains. A kidney biopsy showed glomeruli with mesangial expansion as well as Congo red positive staining of glomeruli, interstitium, and vessels. Electron microscopy showed mesangial deposition of fibrillary material consistent with AL kappa light chain renal amyloidosis. Prior to follow up with Hematology, he was re-hospitalized for AKI, acute liver injury concerning for hepatic amyloidosis and progressive dysphagia likely due to gastrointestinal involvement. Therapy was initiated with bortezomb and dexamethasone; however, no significant kidney recovery was observed, and he remained dependent on dialysis. Due to rapid clinical decline, additional chemotherapy was not offered, and he was transitioned to comfort care.

**Discussion:** This patient presented with dysphagia, persistent hypercalcemia, renal insufficiency and proteinuria highlighting the clinical variability of systemic amyloidosis. As such, systemic amyloidosis, a rare infiltrative disorder, requires a high level of clinical suspicion in order to reach an early diagnosis and prevent long-term complications and mortality associated with advanced, multi-organ involvement. In addition, it is crucial to exclude coexisting multiple myeloma in patients presenting with hypercalcemia, renal insufficiency and AL amyloidosis.

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**PO1906**

Will the Real Creatinine Please Stand Up? Elevated Creatinine in a Patient with Smoldering Myeloma

Evan Zeitler. UNC Kidney Center, Chapel Hill, NC.

**Introduction:** Monoclonal gammopathies cause altered kidney function by a variety of mechanisms. The assessment of patients with monoclonal proteins is further complicated by non-physiologic alterations in laboratory assays, including the assessment of serum creatinine, as reported in this case of a patient with smoldering myeloma.

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**Case Description:** A 47 yo woman with a history of mixed connective tissue disease, hypertension, and IgG lambda light chain smoldering myeloma was referred for evaluation of creatinine of 1.6 mg/dL. Her medications were acetebulotol, furosemide, hydrochlorothiazide and aspirin. Examination revealed BP 129/86, HR 60 without notable physical findings. Her laboratory evaluation was significant for a creatinine of 0.88 mg/dL, BUN of 10 mg/dL, albumin of 4.6 g/dL and total protein of 9.0 g/dL, with an M-spike of 0.1 g/dL. Her urine protein-creatinine ratio was 0.47 g/g creatinine. Over the next year, creatinine at her primary oncologist ranged from 1.2-1.3 mg/dL (except for a single episode of acute kidney injury), while in the nephrology clinic the creatinine was 0.8-0.9 mg/dL. Further investigation determined that the external lab used a picric acid-based creatinine assay, while creatinine from the nephrology clinic was measured using an enzymatic method.

**Discussion:** Monoclonal proteins have previously been reported to interfere with creatinine assays, primarily in patients with Waldenstrom’s macroglobulinemia. We report here a patient with a monoclonal IgG lambda paraprotein interfering with a Jaffe-based creatinine assay leading to pseudohypercreatininemia. Both nephrologists and oncologists should be aware of this phenomenon in the care of patients with all types of paraproteinemias, so that alternative means of kidney function assessment (such as measurement of cystatin c) can be employed when creatinine assays are unreliable.

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**PO1907**

A Unique Case of Light Chain Proximal Tubulopathy

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**Introduction:** Light chain proximal tubulopathy (LCTP), a rare form of monoclonal gammopathy of renal significance (MGRS), is characterized by the accumulation of monotypic light chains within proximal tubular cells. LCTP may present in multiple ways, including acute kidney injury, chronic kidney disease (CKD), Fanconí’s syndrome, and proteinuria. We present a case of LCTP, presenting with CKD and non-nephrotic range proteinuria (NNRP).

**Case Description:** A 62 year old Caucasian male with a past medical history of IgM kappa light chain monoclonal gammopathy of undetermined significance (MGUS) presented for evaluation of CKD. Serum creatinine at the time of initial presentation was 1.4 mg/dL, which correlated with an estimated GFR of 54. No other electrolyte derangements were present. Urinalysis was negative for glycosuria, pyuria, or hematuria with unremarkable urine microscopy. He had NNRP on spot quantification of approximately 400 mg/g creatinine and 32 mg/g of this proteinuria was albuminuria. There was no history of hypertension or diabetes, and he denied NSAID use. He was taking no medications felt to cause chronic interstitial nephritis. Renal ultrasound was unremarkable, and 24 hour ambulatory blood pressure monitoring documented normal BP levels, on no medications. At follow up, the patient’s creatinine fluctuated between 1.4-1.6 mg/dL, and his proteinuria between 400-600 mg/g creatinine. Renal biopsy was pursued because there was no apparent cause to explain his CKD. Biopsy revealed numerous kappa light chain crystalline structures within proximal tubular epithelial cells by immunofluorescence staining of paraffin sections, after pronase-digestion. There was no other evidence of multiple myeloma or Waldenstrom’s macroglobulinemia on prior bone marrow biopsy. He subsequently began therapy with benandmustine and rituxinab.

**Discussion:** We present a case of LCTP manifesting as CKD G3a A1-2. The case was indolent in nature, but was confirmed on renal biopsy using paraffin digestion to prove monoclonality of the crystalline deposits. This led to the diagnosis of a MGRS, and necessitated initiation of chemotherapeutic agents. LCTP is a rare manifestation of MGRS, and might not have been recognized in this case if suspicion had not been high, and biopsy had not been pursued.
Deceiving Schistocytes
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Introduction: Myelodysplastic syndrome (MDS) is a clone bone marrow disorder characterized by dysplasematopoesis, which may manifest as cytopenias and non-immune hemolytic anemia. Schistocytes are commonly associated with causes of microangiopathic hemolytic anemia (MAHA), however, it is rare to have a high reticulocyte count in the peripheral blood smear is a rare and unusual manifestation of MDS.

Case Description: We report the case of a 63-year-old male who presented with complaints of asthenia, fatigue and malaise for the past 3 months. His previous medical history included a past of heavy smoking, arterial hypertension and grade 3 chronic kidney disease (CKD) developed after nephrectomy due to urothermal carcinoma in 2012. He also had in situ papillary urothelial carcinoma of the bladder in 2016, with a course of intra-vascular mitomycin. Vital signs were normal and physical examination was unremarkable. Blood work revealed macrocytic anemia (hemoglobin 7.2 g/dL; MCV 101 fL) and thrombocytopenia (77,000/µL and peripheral blood smear demonstrated 16% schistocytes, with normal coagulation tests, lactate dehydrogenase and lactoglobin. Coombs test was negative. Renal function was stable and there was no evidence of hematooproteinuria. Inflammatory markers were negative. A diagnosis of microangiopathic anemia was assumed and the patient was started on daily plasmapheresis and steroids, while further investigation was under way. Folate and cobalamin levels were normal, anti-nuclear antibodies and HIV, hepatitis B and C serologies were negative and full-body CT scan did not show signs of occult malignancy. Levels of f3 and f4 were also within the normal range. ADAMS-13 activity was 21%. No clinical or analytical improvement was noted after 6 sessions of plasmapheresis (platelet count nadir of 38,000/µL and persistence of schistocytosis). Bone marrow biopsy was performed and a diagnosis of refractory anemia with excess blasts was made.

Discussion: Hemolytic anemia is a common occurrence in patients with hematologic malignancies, particularly acute and chronic myeloid leukemia, but are rarely observed in MDS, with only a few cases reported in the literature. This case highlights the importance of considering a diagnosis of MDS in patients presenting with refractory cytopenias and MAHA.

PO1910
A Case of Oncogenic Osteomalacia with Urinary Phosphate Wasting Masked by AKI
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Introduction: Hypophosphatemia in patients with oncogenic osteomalacia (OO) is due to excess production of fibroblast growth factor 23 (FGF-23) causing urinary phosphate wasting. However, in patients with coexisting acute kidney injury (AKI), hypophosphatemia may normalize as the AKI worsens potentially masking renal phosphate wasting. In-appropriately low or normal phosphorous levels in patients with AKI should prompt further work up to identify potential renal phosphate wasting.

Case Description: 36-year-old morbidly obese woman presented with right-sided abdominal pain and fatigue for 2 weeks. Initial laboratory evaluation revealed AKI (Cr 2.1 mg/dL, baseline 1.2) that failed IV fluid therapy prompting nephrology consultation. Other labs included urine protein creatinine ratio 0.2 g/g, alkaline phosphate (895 U/L), mild hyperbiltrubinemia (1.8 mg/dL), mild hypercalcemia (corrected Ca 11.2 mg/dL), hyperphosphatemia (1.8 mg/dL), low vitamin D (28 ng/mL), normal PTH (19 pg/mL), normal PTHrP (2.2 pmol/L) and low normal calcitriol (28 pg/mL). Kidney ultrasound was normal. Liver ultrasound revealed an ill-defined mass not seen in CT scan. FGF-23 levels were sent due to suspicion of OO and returned very high at 12,715 IU/mL. Patient was readmitted to the hospital for accelerated work up to identify the source of FGF-23. Repeat labs on admission showed Cr of 2.2 mg/dL, normal phosphorous 3.2 mg/dL and bilirubin 12 mg/dL. Random liver biopsy showed tumor cells positive for CD56 and Ki-67, with a proliferation rate of 80% indicating high grade metastatic neuro endocrine tumor. Localization of primary tumor was unsuccessful. Oncology was consulted and chemotherapy was entertained, but the patient rapidly deteriorated and opted for comfort measures.

Discussion: Reduced phosphate excretion in patients with AKI leads to hyperphosphatemia, stimulating FGF-23 production to facilitate phosphaturia. However, when AKI is associated with inappropriately low or normal phosphate levels, renal phosphate wasting from other causes should be suspected. Fractional excretion of phosphate might also be falsely low as the decreased eGFR can potentially hinder phosphate excretion. Early detection and accelerated work up could potentially lead to early diagnosis and appropriate treatment.

PO1911
Lysozyme Nephropathy: A Rare Yet Treatable Cause of AKI in Chronic Myelomonocytic Leukemia
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Introduction: Lysozyme is a small lytic enzyme with bactericidal properties synthesized by monocytes that is freely filtered by the glomerulus. It can be produced in large quantities by neoplastic cells of monocytic lineage resulting in nephrotic range proteinuria (lysozymuria). Lysozyme can accumulate in proximal tubular cells thereby causing toxic injury resulting in tubular cell injury. A 69 year old woman was referred to nephrology clinic for evaluation of elevated serum Cr. Her past medical history included Type-2 Diabetes Mellitus, Hypertension, Hyperlipidemia, JAK2/V617F-positive Polycythemia Vera, Chronic Myelomonocytic Leukemia, bilateral renal angiomylipomas and gout. Physical examination was unremarkable. Lab data were notable for creatinine (Cr) 1.7 mg/dL (baseline 1.2), Calcium 11.1 mg/dL, Uric acid 7.7 mg/dL, WBC 65.1 x 1000/µL (ANC 40.4; Monocytes 14.3); Hemoglobin 11.6 g/dL and Platelets 141 x 1000/µL. Electrolytes, liver function tests, and viral hepatitis serologies were within normal limits. Urinalysis was unremarkable. Urine albumin/Cr ratio was 79.4 mg/g of creatinine. A kidney biopsy was performed. Light microscopy revealed focal acute tubular injury and PAS-positive cytoplasmic granules. Electron microscopy revealed electron dense aggregates in the cytoplasm of the proximal tubular cells. Serum lysozyme was > 60 mcg/mL (reference range 5-11 mcg/mL). A diagnosis of lysozyme-induced nephropathy (LyN) was made. Repeat bone marrow biopsy revealed myeloid neoplasia with 13% blasts. She started treatment with Deoxiabine/Cedazuridine and her WBC improved to < 10 x 1000/µL and her Cr improved to 1.2 mg/dL.

Discussion: This case demonstrates an uncommon and often under-recognized cause of acute tubular injury in patients with chronic myelomonocytic leukaemia. Lysozyme-induced nephropathy can be reversed with targeted therapy.
Light microscopy revealed focal acute tubular injury and PAS-positive cytoplasmic granules (PAS stain).

PO1912

Lymphomatous Infiltration of the Kidney in a Patient with Waldenstrom Macroglobulinemia
Prasanth Ravipati, Lihong Bu, Zohar Sachs, Patrick H. Nachman. University of Minnesota Twin Cities, Minneapolis, MN.

Introduction: Kidney disease can be an initial presentation or a chronic manifestation of plasma cell dyscrasias. The aim of this case report is to illuminate a rare presentation of kidney disease driven by lymphomatous infiltration of the kidney in a patient with Waldenstrom’s Macroglobulinemia (WM).

Case Description: A 70 year old female with an 8 year history of WM (IgM, kappa) was referred for declining renal function. Four months prior to presentation, she had stable WM disease activity and was without symptoms of worsening disease burden. In November of 2020, she was hospitalized with SARS-CoV-2 infection with respiratory failure and acute kidney injury (AKI). Her serum creatinine (sCr) peaked at 3.7 mg/dL from a baseline of 0.9 mg/dL, but recovered to a sCr of 1.1 mg/dL by the time of discharge. Two weeks after discharge, her renal function began to decline prompting nephrology referral. Her sCr had risen to 1.9 mg/dL and she had new onset proteinuria of 1.5 g/day.

Discussion: WM is an uncommon hematologic malignancy, and extramedullary involvement is rare. Only 7% of a cohort of patients with WM who underwent kidney biopsy had lymphomatous infiltration of the kidney [Higgins et al., CJASN 2018]. In our case, the differential diagnosis was broad given the patient’s modest proteinuria and biopsy had lymphomatous infiltration of the kidneys [Higgins et al., CJASN 2018]. In our case, the differential diagnosis was broad given the patient’s modest proteinuria and biopsy had lymphomatous infiltration of the kidneys [Higgins et al., CJASN 2018].

PO1913

Beware of the “B” Type B Lactic Acidosis and Atypical Renal Interstitial Infiltrate
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Introduction: Lactic acid is an endogenous substrate for gluconeogenesis produced by muscle and other tissues. Lactate is the anion of lactic acid and is a source of base that Kreb’s cycle. Lactic acid levels can increase due to impaired oxygen delivery (type A) or impaired oxygen utilization by cells (type B). Here we describe a patient with an unusual presentation of lactic acidosis, and atypical renal interstitial infiltrate.

Case Description: A 32-year-old female with a history of chemotherapy and allogeneic bone marrow transplant in 2018 due to pre-B cell acute lymphoblastic leukemia (ALL) presented with concerns of sepsis due to suspected appendicitis and enlarged kidneys (14 cm on renal ultrasound) which was suggestive of significant interstitial nephritis and tubulitis. Further immunohistochemical stains ordered due to suspicion of ALL reoccurrence, showed a mixture of CD3 and CD20-positive lymphocytes as well as CD68-positive cells. The atypical interstitial infiltrate was positive for CD10, CD45, CD79a, TDT, zebrafish-5, consistent with B-cell leukemia. Flow cytometry and bone marrow biopsy confirmed the relapse of pre-B cell ALL. The patient was treated with steroids and bimatanol, resulting in improvement in kidney function and resolution of lactic acidosis.

Discussion: Although our patient had lactic acidosis and AKI in the setting of presumed sepsis, a common clinical presentation, she had a completely different diagnosis. Her persistent lactic acidosis and atypical interstitial infiltrate led to the diagnosis of relapsed ALL with kidney involvement. Malignancy causes Type B lactic acidosis due to increased tumor lactate production and accumulation, because of the Warburg effect of tumor cells’ metabolism, overexpression of cellular glycolytic enzymes, mitochondrial dysfunction, thiamine, and riboflavin deficiency. Tumor cells have a high rate of glucose uptake and preferential production of lactate, even in the presence of oxygen, known as “Warburg effect.” Type B lactic acidosis from malignancy overall portends a poor prognosis. The goal of therapy is to target the underlying malignancy.

PO1914

A Case of Hemophagocytic Lymphohistiocytosis (HLH) due to Large B Cell Lymphoma with infiltration in the kidneys
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Introduction: Secondary HLH is a life-threatening manifestation of certain malignancies and prompt diagnosis is essential in preventing poor outcomes. Kidney involvement in Large B cell lymphoma is under-reported and diagnosis can be challenging in the absence of abnormal kidney function.

Case Description: A 55-year-old male with no significant history was admitted to our facility with worsening mental status. He had 2 prior hospitalizations at an outside facility where he was treated with steroids for a presumed auto-immune CNS syndrome and partial improvement in symptoms. Vitals signs were normal on arrival and he was non- verbal on exam with right sided weakness. Lumbar puncture was negative for infection or malignant cells on analysis. MRI brain showed contrast enhancing lesions. Hospital course was complicated by acute renal failure and a rise in Serum creatinine in serum creatinine (sCr) 1.5 mg/dl on day 4 of admission in addition to new worsening thrombocytopenia and evidence of ongoing hemolytic anemia. Urinalysis revealed hematuria, no proteinuria, few WBCs but no active sediment. Other lab parameters were relevant for LDH of 3800, Ferritin >3800, TO and T3 levels above normal, soluble IL-2 receptor (sIL-2R) elevated at 33,300. Patient met clinical criteria for HLH with concerns over a thrombotic microangiopathy (TMA) related to HLH and therefore a kidney biopsy was performed which revealed a diffuse atypical lymphohistiocytic infiltrate, consistent with large B-cell lymphoma. No evidence of TMA was seen. A bone marrow biopsy performed at the time confirmed diffuse large B cell lymphoma with pleomorphic features and extensive involvement. A diagnosis of HLH secondary to Large B-Cell Lymphoma with infiltration to the bone marrow & kidneys was made. The patient’s clinical condition deteriorated, and continuous form of renal replacement therapy was started in ICU. Chemotherapy was initiated, however he remained critically ill with worsening lactic acidosis, multi-organ failure and ultimately expired from cardiopulmonary arrest.

Discussion: Malignancy associated HLH is a challenging diagnosis which is often misdiagnosed. Diffuse large B cell lymphoma infiltrating the kidney confers a poor prognosis and this case illustrates the utility of a kidney biopsy in early diagnosis of a diffuse lymphoproliferative disorder which can improve patient outcomes.

PO1915

A Unique Case of Paraneoplastic Lupus Nephritis Biopsy Finding in a Patient with Head and Neck Cancer
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Introduction: Rheumatic disease can be one of manifestations of paraneoplastic syndrome. We present a case of supraglottic squamous cell carcinoma (SCC) associated nephrotic syndrome and kidney biopsy suggestive of lupus-like changes.

Case Description: 56-year-old male with past medical history of hypertension, opioid abuse (methadone) and an active smoker was admitted to the hospital for evaluation of painful neck swelling which he first noticed four days prior to admission. Examination was remarkable for lower extremity edema and left neck mass. Nephrology was consulted for evaluation of nephrotic syndrome. Significant laboratory workup revealed proteinuria: serum albumin: 3.6 g/dl, serum creatinine: 1.4 mg/dl and a normal serum creatinine 0.9 mg/dl. Serological workup for proteinuria including phospholipase A2 receptor antibody (PLA2R Ab) was negative. Biopsy of the neck subcutaneous fat was negative for suppurative squamous cell carcinoma. Subsequent biopsy revealed with carbolplatin and radiotherapy. A kidney biopsy was done for further evaluation. While there were no glomerular changes on light microscopy, immunofluorescence (IF) showed full house capillary staining (IgG, IgM, C3, C1q, kappa and lambda light chains). Also, enhanced glomerular staining for PLA2R was seen. Electron microscopy showed subepithelial deposits and electrondense deposits just like finding on IF, serologies were tested and were negative. Given absence of systemic symptoms of lupus, negative serologies and negative PLA2R Ab, presumed diagnosis of membranous glomerulonephritis secondary from malignancy was made. He was treated consensually with diuretics, angiotensin convertase inhibitor and anticoagulation for thromboembolism prevention. Treatment improved with above treatment, however patient expired due to tumor complications and metastasis.

Discussion: Paraneoplastic systemic lupus erythematosus has been reported in patients with solid tumors. Prognosis with hypothyroidism is the response of self- tolerance antigens, which causes generation of auto antibodies. Auto immune disease usually precedes the diagnosis of malignancy and patients develop symptoms later. Our
case is unique, although biopsy was indicative of lupus nephritis, patient had no clinical or laboratory finding for lupus. Nephrologist and rheumatologist should be aware of this rare clinical association for appropriate diagnosis and management.

POI916
Light Chain Deposition Disease (LCDD) in the Setting of Smoldering Myeloma (SM)

Introduction: Only 50-60% of patients with LCDD meet the criteria for multiple myeloma (MM). SM, a proliferative plasma cell disorder is a precursor for active symptomatic MM. As LCDD is rare, there is limited data for the treatment of LCDD in the setting of SM.

Case Description: A 49-year-old female was found to have proteinuria and microscopic hematuria during a routine workup. Further evaluation showed proteinuria of 4.0 g/day, serum creatinine of 1.3 mg/dL, kappa light chain (KLC) 94.7 mg/mL, lambda light chain (LKC) 1.57 mg/mL, kappa-lambda ratio (K/L) 60.24, Hemoglobin 12.8 g/dL, Calcium 9.26 mg/dL. Kidney biopsy showed nodular mesangial expansion with mild hypercellularity. Moderate tubular atrophy and interstitial fibrosis. Immunofluorescence showed strong kappa staining of mesangium, glomerulus, and tubular basement membrane (TBM) with negative lambda staining. Electron microscopy showed the presence of subendothelial, mesangial, and TBM electron dense deposits. Findings were considered to be consistent with kappa associated LCDD. Bone marrow biopsy showed monoclonal plasma cell population in the bone marrow (5% by flow cytometry and 10-15% by CD138 stain) consistent with smoldering myeloma. FISH was abnormal for monosomy of 13 and 11,14 translocation. The skeletal survey was negative for any lytic lesions. She was treated with Tocilizumab/Dexamethasone/Cyclophosphamide based regimen weekly for 8 weeks which resulted in a decrease in KLC to 1.45 mg/mL, LKC to 1.0 g/dL, and K/L ratio to 1.45 with negative serum immunofixation. 24-hour urine protein improved to 2.6 g/dL. Serum creatinine remained stable at 1.3 mg/dL. Bone marrow biopsy after chemotherapy showed residual plasma cell myeloma involving 5% of the marrow cells. She underwent high dose melphalan followed by Autologous Stem Cell Transplantation (HDM/ASCT). Follow-up labs six years later confirmed successful treatment with serum creatinine improving to 1.02 mg/dL, 24hr-urine protein 484mg/d without microscopic hematuria. SPEP and UPEP remain negative.

Discussion: We report a case of successfully treated LCDD with high dose chemotherapy followed by HDM/ASCT in the setting of smoldering myeloma with six years of follow-up. Patients with LCDD in smoldering myeloma may benefit from high dose chemotherapy along with HDM/ASCT and it should be considered a treatment option.

POI917
Delayed Thrombotic Microangiopathy Post Bone Marrow Transplant, an Atypical Presentation: A Case Report
Vikas Vujjini, Aman Deep, Matthew Palmer, Abdullah Sassine Garea. Penn Medicine, Philadelphia, PA.

Introduction: Thrombotic Microangiopathy (TMA) is a potentially lethal complication of Bone Marrow Transplantation (BMT). We report a case of delayed TMA post-BMT which was successfully treated with Rituximab.

Case Description: A 53-year-old male known to have hepatosplenic gamma-delta T-cell lymphoma (HSTCL) was referred for evaluation of worsening creatinine. He was diagnosed with HSTCL 6 years ago that was refractory to multiple therapies, and ultimately, two years later, he received Double Unit Cord Blood (dUCB) transplantation with good response and minimal residual disease. Despite receiving tacrolimus and mycophenolate mofetil (MMF) for prophylaxis of Graft versus Host Disease (GVHD), he developed mild popular rash consistent with Grade I GHVD skin and recurrent pneumonitis concerning for lung GVHD which responded to steroids. The tacrolimus and MMF were discontinued and steroids were gradually tapered off. Eight months post-transplant, serum creatinine (sCr) started to gradually increase from a baseline of 1.0 mg/dL. We were consulted eighteen months post-dUCB when sCr reached 1.8 mg/dL. Additional evaluation showed mild proteinuria (UPCR 0.77 g/g of creatinine), no active urine sediment, low haptoglobin (< 30 mg/dL) and worsening thrombocytopenia (105 x 10^9/L). A renal biopsy showed glomeruli with variable capillary wall thickening and double contours, moderate fibrosis of 40-50%, negative immunofluorescence for complement and immunoglobulin, and the electron microscopy showed subendothelial expansion and endothelial swelling. These findings were compatible with chronic TMA lesion concerning for renal GVHD. The patient was treated with weekly Rituximab 375 mg/m² for a total of 4 doses with stabilization of sCr and normalization for hemolysis labs, including normalization of platelet count.

Discussion: TMA is a well described complication post-BMT with multifactorial etiology (medication, GVHD, radiation, etc.) with early onset within the first 30-45 days after transplantation, and the mortality rate is approximately 30-80%. Our patient had the unusual delayed presentation post-BMT (after 18 months). Although historically not the first line, several case reports have been published showing use of Rituximab, an anti-CD20 monoclonal antibody, with positive response.

POI918
A Rare Case of Monoclonal Gammapathy of Renal Significance
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Introduction: Monoclonal gammapathy of renal significance represents a group of disorders in which monoclonal immunoglobulin secreted by a non malignant or premalignant B cell or plasma cell clone causes renal damage. These disorders do not meet diagnostic criteria for multiple myeloma or lymphoproliferative disorder.

Case Description: 64 year old female with hx of hypertension, presented to ED for worsening lower extremity edema, dyspnea. She was admitted for CHF exacerbation. Admission creatinine was 2.0 (prior baseline 1.0). She developed resistance to diuretics with worsening renal failure requiring dialysis. She had 6.0 grams of proteinuria. Kidney biopsy showed ATN, and findings consistent with PGNMIG with IgGk. She had spep/ upep/free light chains ratio which were all normal. Bone marrow biopsy was normal. Since no clone had been identified to guide treatment, plan made to treat her with bortezomib, cytoxan and dexamethasone.

Discussion: -PGNMIG is a monoclonal gamopathy which resembles immune complex GN - Most common pattern seen in PGNMIG is IgGk (this is more nephroticigenic and has ability to activate compliment cascade causing inflammatory damage. Majority of the patient with PGNMIG do not have clone identified. In such patients treatment is empiric with bortezomib/cytoxan/dexamethasone or rituximab.
Review of Onconephrology Cases: An Insight from the Middle East

Objectives: The purpose of this study was to present an overview of cancer-related kidney injury (CRI) at a tertiary center in the Middle East and to highlight common preventable causes of AKI and their outcome in this patient population.

Methods: We conducted a retrospective observational study of 39 admitted cancer patients referred to the department of Nephrology between November 2020 and March 2021. Inclusion criteria were patients with cancer admitted to the department of Nephrology with AKI. The exclusion criteria were patients who were transferred to the department of Nephrology for AKI due to other causes; the most common being sepsis. We collected data on demographic characteristics, history of cancer, and cancer-related treatments that were associated with the development of AKI. The causes of AKI were classified into primary and secondary categories. The primary causes were drug-induced AKI, hypercalcemia, and hypovolemia, and the secondary causes were sepsis, obstructive urinary tract disease, and acute interstitial nephritis.

Results: The most common primary causes of AKI were drug-induced AKI (33%), hypercalcemia (7%), and hypovolemia (7%). The most common secondary cause of AKI was sepsis (30%). The most common histological diagnosis in the group of patients with AKI was chronic kidney disease (23%). The most common histological diagnosis in the group of patients without AKI was chronic kidney disease (38%). The most common histological diagnosis in the group of patients with AKI was chronic kidney disease (23%). The most common histological diagnosis in the group of patients without AKI was chronic kidney disease (38%).

Conclusion: The study demonstrates the importance of early recognition and prompt management of risk factors. This study prompts the need for further research to improve the understanding of the mechanisms underlying AKI in cancer patients.
Methods: To identify RG genes suitable as internal controls in human non-cancerous kidney tissue, we selected 18 RG candidates based on previous data and screening in 30 expression datasets (>800 patients), including our own, publicly available or provided by independent groups. Datasets included specimens from patients with hypertensive and diabetic nephropathy, Fabry disease, focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, and minimal change disease. We examined both microdissected and whole section-based datasets. Expression variability of 4 candidate genes (YWHAZ, SLC4A1AP, and ACTB) was further examined by qPCR in biopsies from patients with hypertensive nephropathy (n=11) and healthy controls (n=5).

Results: Only YWHAZ gene expression remained stable in all datasets whereas SLC4A1AP was stable in all but one Fabry dataset. All other RGs were differentially expressed in at least 2 datasets, and in 4.5 datasets on average. No differences in YWHAZ, SLC4A1AP, RPS13 and ACTB gene expression between hypertensive and control biopsies were detected by qPCR.

Conclusions: Although RGs suitable to all techniques and tissues are unlikely to exist, our data suggest that in non-cancerous kidney biopsies expression of YWHAZ and SLC4A1AP genes is stable and suitable for normalization purposes.

PO1924

Comparison of Proteomic Methods in Evaluating Biomarker-AKI Associations in Cardiac Surgery Patients

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Background: Although immunoassays are the most widely used protein measurement method, aptamer-based methods such as the SomaScan platform can quantify up to 7,000 proteins in a single sample and have showed strong concordance with immunoassays. However, they may have different disease associations, but interpretation of results should keep in mind a broad range of factors that can affect the results, including %CVs of both platforms and storage time. We compared across 30 preop and 34 postop immunoassay-aptamer pairs. Possible correlations with immunoassays.

Methods: In a substudy of the TRIBE-AKI cohort, preop and postop plasma samples from 294 patients with previous immunoassay measurements were analyzed using the SomaScan platform. Inter-platform Spearman correlations (rs) and AKI associations were measured and used as standards for side by side MSI analysis of any dataset. The correlation of 13 proteins preop and 24 postop, with other factors were found, including %CVs of both platforms and storage time. We observed a strong association between rs and biomarker molarity, with Spearman correlation 0.64 preop and 0.53 postop. No strong associations exist, our data suggest that in non-cancerous kidney biopsies expression of YWHAZ and SLC4A1AP genes is stable and suitable for normalization purposes.

PO1925

Performance of Creatinine-Based Equations to Estimate Glomerular Filtration Rate in the Context of Drug Dosage Adaptation


Background: The 1976 Cockcroft-Gault (CG) creatinine-based equation is still used to estimate GFR (eGFR) for dose adaptation of drugs excreted by glomerular filtration although it estimates creatinine clearance. It was developed based on non-standardized creatinine assays and is not recommended by any nephrology guidelines. Incorrect eGFR may lead to hazardous over- or underdosing. We aimed to compare the performance of CG with modern equations based on standardized creatinine assays.

Methods: In a cross-sectional analysis CG was validated against measured GFR (mGFR; using various tracer methods) in 15,479 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), Lund-Malmö-Revised (LMR), and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision and accuracy (percentage of estimates within ±30% of mGFR, P30) overall and stratified for mGFR, age and body mass index intervals at mGFR <60 mL/min, as well as classification in mGFR stages.

Results: The CG equation performed worse than the other equations, overall in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy (P30 overall for CG/MDRD/CKD-EPI/LMR/CKFC 73.6%/51%/82%/84%/87%/85%/(86.9%) except for patients ≥65 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. At BMI [18.5-25] kg/m2, all equations performed similarly and at BMI-[18.5-25] kg/m2, CG and LMR had the best results though all equations had poor P30-accuracy (CG/LMR 58.7%/57.2%). At BMI≥25 kg/m2, bias of CG increased with increasing BMI (+19.3 mL/min at BMI≥40 kg/m2). The four more recent equations also classified mGFR stages better than CG.

Conclusions: The CG equation exhibited worse performance to estimate GFR overall and in analyses stratified for GFR, age, and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.

PO1926

Human Kidney Mimetic Tissue Using Endogenous Lipids and Metabolites as Standards for Quantification and Quality Control

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Background: Mass spectrometry imagine (MSI) determines the spatial localization of numerous species directly from the sample and has been heralded in tissue analysis. However, majority of studies have not been quantitative and reproducible. The presentation of a quantified tissue distribution has distinct benefits over the common approach of quantifying the tissue homogeneous especially if tissue distribution is heterogeneous, making overcoming this limitation a top priority.

Methods: An improved mimetic tissue mold has been developed. Briefly, human kidney tissue was cut into small pieces and spiked with a normalization standard (lysop-PAF), an antioxidant, and a phospholipase A2 (PLA2) inhibitor to protect endogenous lipids and metabolites from the most common degradation. Lipidomic and metabolomic analyses of this mimetic tissue were performed, and the absolute amounts of various compounds were measured and used as standards for side by side MSI analysis of any tissue sample of interest. Since stabilizers are used, the quantitative data of the mimetic tissue are reliable and can be used as quality control (QC) tracers to tissue samples during storage and shipment.

Results: Mimetic tissue molds were prepared by spiking stable isotope labeled compounds at different concentrations layer by layer for validation. Initial validation experiment found that: a) MSI can detect the concentration differences with acceptable linearity, accuracy, and repeatability; b) Spiking of high concentrations affects the endogenous signals; c) It’s not practicable to spike each compound for its quantification due to signal suppression, high material and labor consumption; d) Using endogenous amounts as reference standards is a suitable approach. To use the homogenized mimetic tissue as a spatial quantitative and QC standard, the endogenous amounts of lipids and metabolites were measured with bulk omics. More than 200 lipids, 25 amino acids, and numinous organic acids were quantified.

Conclusions: Quantifying endogenous lipids and metabolites using bulk methods as MSI quantification standards is innovative in the field. The similarity of tissue matrix and targeting compounds between mimetic and sample tissues can provide more meaningful and reliable results.

Funding: NIDDK Support
Comparison of Aptamer-Based and Antibody-Based Assays for Protein Quantification in CKD

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Background: Novel aptamer-based technologies can identify over 7000 analytes per sample, offering a high-throughput alternative to traditional immunoassays in biomarker discovery. However, the specificity for distinct proteins has not been thoroughly studied in the context of chronic kidney disease (CKD).

Methods: We aimed to validate the use of SOMAscan, an aptamer-based technology, for the quantification of 8 immune activation biomarkers and cystatin C in 498 participants from the African American Study of Kidney Disease and Hypertension (AASK) using immunoassays as the gold standard.

Results: Six biomarkers (IL-8, TNFRSF1B, cystatin C, TNFRSF1A, IL-6 and suPAR) had moderate-to-high correlations (Pearson r = 0.22 to 0.94, Spearman r = 0.30 to 0.98), between SOMAassay and immunoassay measurements and three (IFN-γ, IL-10 and TNF-α) were uncorrelated (r = 0.03 to 0.10, r = 0.03 to 0.06). Of those with moderate-to-high correlations, TNFRSF1B, cystatin C, TNFRSF1A, and suPAR were negatively correlated with iothalamate-measured GFR and associated with higher risk of ESKD. All 6 biomarkers with moderate-to-high correlations were associated with increased risk of mortality. On average, immunoassay measurements were more strongly associated with adverse outcomes than their SOMAassay counterparts (Figure).

Conclusions: SOMAscan is an efficient and relatively reliable technique for the quantification of biomarkers in the setting of CKD and for the detection of potential associations with clinical outcomes. Targeted immunoassays of candidate proteins may provide additional prognostic information.

Funding: NIDDK Support

Prescribed Sodium Bicarbonate and Incident CKD in US Veterans

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Background: Sodium bicarbonate is prescribed for a variety of medical conditions including treatment of hypocarbonatemia that may happen in the setting of metabolic acidosis or due to other pathologies. Hypocarbonatemia is usually observed with chronic kidney disease (CKD) when eGFR < 60 mL/min/1.73 m2 and is uncommon without established CKD (eGFR > 60 mL/min). It is not known whether incident sodium bicarbonate prescription in patients with normal kidney function is associated with adverse outcomes including de novo chronic kidney disease, which we sought to examine in a large national cohort of Veterans.

Methods: In 2,524,842 US Veterans with normal baseline eGFR (≥60 mL/min/1.73m2) and available data on albuminuria in 2004-2006, we examined the association of de novo prescription of bicarbonate medications during the baseline period with incident CKD over 14 years. Associations were examined in hazard models adjusted for demographics, major comorbidities, baseline eGFR, and albuminuria category.

Results: We identified 759 Veterans who were incident bicarbonate users. Overall, patients were a mean 61±14 years old, 7% female, 16% Black, and 5% Hispanic. Bicarbonate users were more likely to be male, Black, smokers, with higher frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, diabetes, and cardiovascular comorbidities. They also were more likely to have albuminuria. Bicarbonate medication users had a 4.8-fold higher risk of incident CKD (HR: 4.81, 95%CI: 4.38, 5.27).

Conclusions: Veterans with eGFR ≥60 mL/min/1.73m2 who were prescribed sodium bicarbonate exhibited nearly five times greater likelihood of incident CKD. Whether bicarbonate therapy is a surrogate of disease condition with higher risk of CKD or whether it causes CKD directly remains to be examined in additional studies.

Funding: Clinical Revenue Support

LRP2-Facilitated Regulation of Mitochondrial Metabolism by Extracellular Cues: Important Roles for Signal Peptides’ Leucines in Protein-Protein Interactions and Signaling

Qinetian Li,1 Michael Holliday,2,3 Jenny S. Pan,1,2 Li Tan,3,1 Jeffery Li,4 David Sheikh-Hamad,1,2 Baylor College of Medicine, Houston, TX; 3Michael E DeBakey VA Medical Center, Houston, TX; 4Sichuan University West China Medical Center, Chengdu, China.

Background: Stanniocalcin 1 (STC1), a mitochondrial intracrine activates mitochondrial anti-oxidant defenses. LRP2/megalin shuttles STC1 to the mitochondria through retrograde early endosome-to-Golgii- and Rab32, and LRP2 KO impairs mitochondrial respiration and glycolysis.

Methods: We determined STC1-LRP2 interaction domains using HA- and FLAG-tagged fragments of STC1 and LRP2, respectively, co-expressed in HEK293T cells.

Results: The trans-membrane domain of LRP2 is required for trafficking to the mitochondria. STC1-FLAG expressed in LRP2 KO cells fails to reach the mitochondria; whereas STC1-FLAG cotransfected with LRP2 wild type or Leucines L8/9/11 does not bind LRP2. Using Seahorse analyzer, STC1 fails to induce mitochondrial respiration and glycolysis.

Conclusions: LRP2 facilitates STC1’s mitochondrial trafficking and the mitochondrial anti-oxidant defenses. LRP2KO KO impairs mitochondrial respiratory and glycolytic function.

Funding: Clinical Revenue Support

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Conclusions: LRP2 facilitates STC1’s mitochondrial trafficking and the mitochondrial anti-oxidant defenses. LRP2KO KO impairs mitochondrial respiratory and glycolytic function.

Funding: Clinical Revenue Support
respiration or glycolysis in megalin KO MEF expressing mutant LRP2, while mutant hSTC1 (L8/L9/L11 -> A8/A9/A11) fails to reach the mitochondria or induce respiration and glycolysis in WT MEF.

**Conclusions:** Our data suggest direct regulation of mitochondrial metabolism by extracellular cues and reveal an important role for signal peptides and their leucines in protein-protein interactions and signaling.

**Funding:** Veterans Affairs Support

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**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG Groups</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of GS, SS and IS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>1.011</td>
<td>1.015</td>
<td>1.016</td>
</tr>
<tr>
<td>Medium grade</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Low grade</td>
<td>0.993</td>
<td>0.997</td>
<td>0.998</td>
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</tbody>
</table>

**Table 4** Logistic regression for TG groups and histopathologic parameters

**PO1931**

**Percutaneous Kidney Biopsy in Outpatient Setting: Can I Go Home Now?**

Ashen K. Zariya,1 Amee Kumar,1 Tyler M. Palombo,2 Prasanti S. Ravipati,2 Diane V. Thompson,1 Khaled Nashar,1 Swati Arora,1

**Background:** Kidney biopsies are a key diagnostic tool in renal dysfunction; however, complications ranging from bleeding to hematoma requiring embolization can occur. There is conflicting evidence on how long to keep patients post-biopsy. Some studies show 100% of serious complications occur within 8 hours, while others show that one-third can occur after 8 hours. Shorter observation periods prevent unnecessary testing and help reduce healthcare costs. Our study aims to assess if patients can be safely discharged with a six-hour observation period post-biopsy.

**Methods:** Single-center retrospective Quality Improvement (QI) study of patients undergoing outpatient percutaneous native kidney biopsy over last 5 years (n=177) divided into 2 groups: Group A: Same-day discharge after biopsy. Group B: 23-hour observation after biopsy. All three patients with bleeding complications had >10% Hb drop within first 6 hours post-biopsy. No readmissions related to biopsy occurred.

**Conclusions:** There were no major complications in either group. This QI study suggests that the majority of asymptomatic patients can be safely discharged at 6 hours post-biopsy if Hb is stable. This could help reduce healthcare costs and burden to patients. This is a limited single-center study: further larger studies are needed to confirm this.

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**Table 5**

<table>
<thead>
<tr>
<th>Bleeding Complications Post-Kidney Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Group B</td>
</tr>
</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: Observational and prospective study of KBs performed in our center during 2019 and 2020. We started a collection of KB samples to biobank at 2019. In 211 patients who accepted, instead of two cylinders, three cylinders were obtained during the procedure. Clinical and laboratory data of patients were reviewed. Risk factors for complications, including the number of cylinders obtained, was also assessed.

Results: In 211 patients in whom we performed a KB at our hospital were included in the biobank. 8 patients(3.6%) underwent trans-jugular renal biopsy, which we have excluded. Of the remaining 213, 126(59.2%) were men, the mean age 56.8±16.9 years, 122(57.3%) patients had hypertension, 46(23%) were diabetics, 14(6.3%) were under anticoagulant treatment and 35(16.4%) under antplatelet treatment. The mean creatinine was 2.22±1.9 mg/dl, protein/creatinine urine ratio 1119.6±2957.9 mg/g, the hemoglobin pre-KB was 12.1±2.3 g/dL, 254380(8873) platelets, INR 0.98±0.09, prothrombin time 11.8±1.16 seconds. 69.5%(n=148) of patients 3 renal cylinders were obtained, 27.2%(n=58) 2 cylinders and in 3.3%(7=1) one cylinder. Minor complications were observed in 13.6%(n=29) and major complications in 3.3%(n=7). We observed that patients with complications in KB were younger(p=0.034), had less weight(p=0.022), more transfusions(p=0.003), more platelets(p=0.038), a lower PT(p=0.005) and 1 cylinder was obtained in the KB with more frequency(p=0.012). In a multivariate regression logistic analysis PT (OR:1.497, p=0.042), transfusions(OR:5.38, p=0.032) and 1 cylinder obtained(OR:7.258, p=0.032) were identified as a risk factors of KB complications.

Conclusions: KB is a procedure with a low complication rate. Obtaining three KB cylinders for biobank has not shown an increase in the rate of complications, which is in concordance with previous published studies remains low.

PO1933
Assessment of Glomerular Number in Fresh Renal Tissue and Renal Pathological Specimens
Kosuke Sonoda, Makoto Harada, Koji Hashimoto, Yuji Kamijo, Shinshu Daigaku, Matsumoto, Japan.

Background: On-site evaluation of fresh renal tissue at the time of renal biopsy is useful. However, some cases present poor correlation in glomerular number between fresh renal tissue and renal pathological specimens.

Methods: To examine the usefulness of on-site evaluation, the correlation between glomerular number in fresh renal tissue and renal pathological specimens, and associated factors disturbing the evaluation were investigated via a retrospective cross-sectional observational study.

Results: In the included 129 cases, there was a significant positive correlation between glomerular number in fresh renal tissue and renal pathological specimens. The median ratio of glomerular number (renal pathological specimen/fresh renal tissue) was 0.74 (0.48–0.97). According to this ratio, all cases were divided into three groups: a reasonable estimation group (65 cases), underestimation group (32 cases), and overestimation group (32 cases). Comparing the reasonable estimation group with the underestimation group, significant differences were detected in the extent of interstitial fibrosis and tubular atrophy (IFTA) and in the extent of interstitial inflammation. Logistic regression analyses also demonstrated that IFTA and interstitial inflammation were significantly associated with underestimation.

Conclusions: In conclusion, glomerular number counted by on-site evaluation of fresh renal tissue estimated the actual number of glomeruli in the renal pathological specimen, suggesting clinical benefit. Since tubulointerstitial lesions, such as IFTA and/or interstitial inflammation, may make it difficult to recognize glomeruli in fresh renal tissue, the possibility of underestimation of results for cases with possible severe tubulointerstitial lesions should be considered.

PO1934
Variability in Estimates of Nephron Number from Biopsy
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Background: Nephron number may predict kidney health and functional capacity. It is unknown whether biopsies can be used to predict glomerular number (Nglomer) in individuals, or how many subjects are required to detect differences between populations. We investigated the accuracy and precision of Nglomer measured from biopsy.

Methods: We examined 6 human kidneys, rejected for transplant. We performed 8-10 needle biopsies. We used this and cortical volume to estimate Nglomer. We simulated 210-594 individuals, or how many subjects are required to detect differences between populations.

Results: Nglomer estimated from single needle biopsy had up to 70% error depending on the frequency distribution of each disease category was evaluated across age categories within demographic subgroup were our primary and secondary outcomes. In addition, the frequency distribution of each disease category was evaluated across age categories stratified by sex and race.

Conclusions: A single biopsy is not sufficient to predict Nglomer in the individual kidney, but this work provides the required number of subjects required to detect differences in Nglomer between populations.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

594

Figure 1. (A) "Virtual biopsy" by 3D CFE-MRI. (i) 3D visualization of single VB with FT-labeled (black dots) and (ii) segmented glomeruli (spheres). Scale =1 mm. (B) Distribution of Ngglomer from (i) physical and (ii) virtual biopsies (VB). (iii) The mean NgglomerSD within the clusters of VB. (iv) Variability in Ngglomer.

PO1935
Epidemiology of Medical Kidney Disease in the Southwestern United States, 1989-2018
Akira Takahashi,1 Takamasa Miyauchi,1 Yi Mi Kevin Ren,1 Toshiki Doi,2 Takao Masaki,3 Michifumi Yamashita,1 Cedars-Sinai Medical Center, Los Angeles, CA; 2Hiroshima University Hospital, Hiroshima, Japan.

Background: Kidney biopsy is the main source of epidemiological information for kidney disease. However, large-scale epidemiological studies for glomerular disease (GD) in the US are very limited, and there are no such studies for non-glomerular disease (non-GD). Here, we describe 30-year temporal and demographic trends in GDs and non-GDs in the southwestern US between 1989 and 2018.

Methods: In this retrospective study, all kidney biopsy data at Pathology, Cedars-Sinai Medical Center (CSMC), Los Angeles, CA, between 1989 and 2018 were reviewed. We analyzed the most common 26 GDs and the most common 9 non-GDs. The frequencies of GD and non-GD subtypes and the temporal trends in each disease subtype within demographic subgroup were our primary and secondary outcomes. In addition, the frequency distribution of each disease category was evaluated across age categories stratified by sex and race.

Results: Among 48,068 patients (mean age =50.3±19.3 y.o.; 52.0% men; 55.5% white; 18.4% Latino; 11.1% black; 9.8% Asian; 5.2% others), GD and non-GD composed 83.4% and 16.6% of all biopsies, respectively. In GDs, the frequency of diabetic glomerulosclerosis increased over the three decades (8.4%, 12.2%, and 22.0% of diagnoses; P for trend =0.003). The frequency of FSGS, lupus nephritis, immune complex-glomerulonephritis (GN), membranous nephropathy, and minimal change disease declined substantially over time. On the other hand, IgAN and ANCA/pauci-immune GN remained stable. In non-GDs, nephrosclerosis was the most frequent in study period. However, acute tubular necrosis/injury slightly increased over time and became the most common subtype in the latest 10 years. These temporal trends were largely preserved within all demographic subgroups, although cross-sectional frequency distributions differed according to age, sex, and race.

Conclusions: We reported the largest epidemiological study of medical kidney disease in the US. The relative renal biopsy frequencies of many GDs and non-GDs showed significant changes over the three decades in the southwestern US. Temporal
PO1936
Pathology Core Scoring Parameters and Reproducibility in the CureGN Study
Abigail R. Smith,1, Matthew Palmer,15 Virginie Royalt,1 Qian Liu,4 Nicole K. Andeen,2 Carmen Avila-Casado,4 S. M. Baginasco,12 Vivette D. Agati,1 Agnes B. Fog,9 Joseph Gauth,10 Rasheed A. Gabudgesin,11 Larry A. Greenbaum,12 Jean Hou,1 Richard A. Lafayette,10 Helen Liapis,10 Afshin Parsa,1 Bruce M. Robinson,1 Michael B. Stokes,14 Katherine Twombly,14 Jarey Zee,10 J. Charles Jennette,10 Cynthia C. Nast.10 Arbor Research Collaborative for Health, Arbor, MI; 2Oregon Health & Science University School of Medicine, Portland, OR; 3Universite de Montreal, Montreal, QC, Canada; 4Columbia University Irving Medical Center, New York, NY; 5Vanderbilt University Medical Center, Nashville, TN; 6Duke University School of Medicine, Durham, NC; 7Cedars-Sinai Medical Center, Los Angeles, CA; 8Stanford Medicine, Stanford, CA; 9National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 10University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; 11University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 12Johns Hopkins University School of Medicine, Baltimore, MD; 13Medical University of South Carolina, Charleston, SC; 14Emory University, Atlanta, GA; 15Washington University in St Louis School of Medicine, St Louis, MO; 16University of Toronto, Toronto, ON, Canada.

Background: CureGN is an NIH-funded multi-center, prospective, observational cohort study of patients with minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA nephropathy from 66 international sites with 2500 enrolled participants. The large scale of CureGN requires a practical systematic approach to pathologic scoring that can be applied consistently across a large number of cases and multiple scoring pathologists. The method reflects common pathology practice: generating data for assignment to current used disease classifications and use in future studies utilizing conventional parameters. The objective of this analysis was to determine and evaluate the pathology scoring reproducibility.

Methods: The CureGN Core Scoring Workgroup established definitions of multiple glomerular, tubular, interstitial, and vascular lesions evaluated, semiquantitatively, and observed by light, immunofluorescence, and electron microscopy (EM). All cases with complete pathology data as of April 2019 were randomly assigned for scoring of whole slide and EM images to one of eleven pathologists; a random subset of >10% were scored by at least one pathologist, 94 were scored twice (12%). Of 60 pathology features, 46 had moderate reproducibility (AC1=0.58), but scored as absent vs present had AC1=0.71. (77%) demonstrated excellent reproducibility (Gwet’s AC1>0.8), and 12 (20%) had good reproducibility. Of 60 pathology features, 46 had moderate reproducibility (AC1=0.58), but scored as absent vs present had AC1=0.71. (77%) demonstrated excellent reproducibility (Gwet’s AC1>0.8), and 12 (20%) had good reproducibility.

Results: Of 797 biopsy specimens (141 MCD, 186 FSGS, 205 MN, 265 IgA) scored by at least one pathologist, 94 were scored twice (12%). Of 60 pathology features, 46 (77%) demonstrated excellent reproducibility (Gwet’s AC1=0.8), and 12 (20%) had good reproducibility (Gwet’s AC1>0.6). Mean hypercellularity was scored as absent, focal or diffuse had moderate reproducibility (AC1=0.58), but scored as absent vs present had AC1=0.71. The percent glomeruli scored as having no lesions had fair reproducibility (AC1=0.34).

Conclusions: The majority of pathologic features scored showed excellent reproducibility, supporting the hypothesis that these features can be scored consistently by multiple pathologists. Future studies will include correlation of these histopathologic features with clinical and demographic characteristics at the time of biopsy and eventually disease biomarkers and clinical outcomes.

Funding: NIDDK Support

PO1937
Dysmorphic Lysosomes, Pathognomonic of Chronic Interstitial Nephritis in Agricultural Communities (CINAC)
Clara Orantes,1 Litia Orantes,1 Nehrita A. Guerra,4 Carlos A. Salinas,4 Carlos Orantes,1 Lilly M. Barba,3 Sami M. Akram,2 Ministry of Health of El Salvador, Santa Ana, El Salvador; 2Loma Linda University, Loma Linda, CA; 3San Juan de Dios Hospital, nephrology department, Santa Ana, El Salvador; 4Harbor-UCLA Medical Center, Torrance, CA.

Background: The etiology and pathogenesis of CINAC are unknown. Two hypotheses have been put forward. Dysmorphic lysosomes (DL) were described as disease biomarkers and clinical outcomes.

Methods: Sixteen patients from Central America, suspected of CINAC clinically underwent kidney biopsy (KB). Demographic characteristics, blood and urine analysis data were collected. Renal histology was studied using light (LM), immunofluorescence (IF), and electron microscopy (EM). We reviewed the literature in PubMed using the following search terms (a). "Chronic Interstitial Nephritis + Electron Microscopy + Kidney" and identified 8 relevant cases (Group A) (b). "Dysmorphic Lysosomes, Electron Microscopy" found 14 cases that described the EM findings (Group C). Results: Of the 16 patients in Group A, only 2 had DL on EM. One patient had Calcineurin Inhibitors (CNI) and one patient from Sri Lanka had chronic kidney disease of unknown origin, which is also considered as CINAC. In patient who had CNI, the DL had irregular edges unlike the smooth rounded DL of varying sizes noted in all CINAC patients. In the control group, C, the patients who had DL, were 14 but the DL were present in organs other than kidneys. The two patients had DL in the kidneys, one was Fabry’s disease, and the other was Light chain Proximal tubulopathy (LCPT). In Fabry’s disease, the DL were lamellated. In LCPT the DL were rectangular due to the characteristics of the lambda proteins.

Conclusions: Dysmorphic Lysosomes may occur in multiple disorders, however, in young persons with agricultural exposure, non-nephritic proteinuria, presence of tubular inflammation, presence of smooth rounded clusters of DL are pathognomonic. Morphology of the DL is dictated by the contents of the lysosomes as in the case of LCPT; further, evaluation is recommended.

Poster

PO1938
Reduction of Globotriaosylceramide Inclusions in Renal Peritubular Capillaries in Patients with Fabry Disease Following Treatment with Pegunigalsidase Alfa
Laura Barisioni,1, J. Charles Jennette,4 Myrl D. Holliday,1 Ozlem Goker-Alpan,4 Gustavo Maegawa,5 Pilar Giraldo,6 Derlis E. Gonzalez,7 Ahmad M. Tufafo,4 Sari Alon,1 Einat Almon,8 Raul Chertkoff,9 Derrylann Hughes,10 Duke University School of Medicine, Durham, NC; 1University of North Carolina School of Medicine, Chapel Hill, NC; 2The University of Iowa Healthcare, Iowa City, IA; 4Lysosomal Disorders Research and Treatment Unit, Fairfax, VA; 5University of Florida, Gainesville, FL; 6Hospital de Dia Quirurg, Zaragoza, Spain; 7Instituto Privado del Nino y Adolescente, Asuncion, Paraguay; 8University of Kansas Medical Center, Kansas City, KS; 9Protalix Biotherapeutics, Carmiel, Israel; 10Royal Free London NHS Foundation Trust, London, United Kingdom.

Background: Fabry disease (FD) is a rare genetic disorder characterized by reduced activity of the lysosomal enzyme α-galactosidase A (α-Gal A), leading to accumulation of sphingolipids such as glycolobiosylceramide (Gb3) and globotriaosylphosphoglycerol (Gb3P), and organ dysfunction. Gb3 inclusion forms in various renal cell types and Gb3 clearance from renal peritubular capillaries (PTCs) has been used as a surrogate endpoint in trials of approved FD therapies. The objective of this analysis was to quantify the reduced burden of Gb3 inclusions in PTCs in patients with FD participating in a phase 1/2 trial of pegunigalsidase alfa (recombinant α-Gal A) enzyme replacement therapy. Methods: In a phase 1/2 dose-ranging study (NCT01678899), 18 adults with FD received 0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg of pegunigalsidase alfa by intravenous infusion every 2 weeks for up to 12 months. Kidney biopsies were taken at baseline and after 6 months of treatment. Levels of Gb3 inclusions in renal PTCs were determined using the Barisoni Lipid Inclusions Scoring System (BLISS) protocol (Barisoni L et al. Arch Pathol Lab Med. 2012;136:816-824).

Results: Of 14 evaluable patients with available kidney biopsies at baseline and 6 months, 12 patients (85.7%) had 20% reduction, 11 patients (78.6%) had ≥50% reduction, and 3 patients (21.4%) had ≥90% reduction in Gb3 inclusions. In the analysis (n=13; excluding 1 male patient due to minimal renal involvement), the mean BLISS score 6 months from baseline was lowered for all doses (reduced by 75.5%, 86.5%, and 39.1% for 0.2 mg/kg, 1.0 mg/kg, and 2.0 mg/kg treatment, respectively). The magnitude of reduction of Gb3 inclusions was greater in males (n=7; reduction: 85.0%) vs females (n=6; reduction: 47.7%). Overall, mean BLISS score was reduced from 4.23 at baseline to ≤3 at 6 months (67.8% vs 8.9%). Reduction in Gb3 inclusions at 6 months was correlated with a reduction in plasma Gb3 at 12 months (R=0.905).

Conclusions: Results from this phase 1/2 study demonstrated that pegunigalsidase alfa reached the affected tissue and effectively reduced the number of Gb3 inclusions in renal PTCs at 6 months in adults with FD.

PO1939
Patients with Active Mantle Cell Lymphoma May Present with Monoclonal, Polyclonal, or C3-Dominant Glomerulonephrites, Which Respond to Lymphoma-Directed Therapy
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Background: There are limited reports on kidney biopsy findings in patients with mantle cell lymphoma (MCL).

Methods: We initiated a multi-institutional, retrospective review of kidney biopsy findings from patients with active and treated MCL.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
**Results:** Twenty-nine patients (31 biopsies) with MCL and kidney biopsies were identified, with a median age of 66 (range 48-87), 76% of whom were men. Nineteen patients had active MCL at the time of biopsy, 13 of which (68%) presented with acute kidney injury, proteinuria and/or hematuria, and biopsy findings attributable to lymphoma (Table); 6 (32%) had findings not readily attributable to MCL. Of the former, 10 (77%) had immune complex (IC) disease including proliferative glomerulonephritis with monotypic IgG deposits (PGNMID, 2), C3 dominant GN (3), PLA2R-negative membranous (MN, 3), and/or tubular basement membrane deposits (2). Lymphomatous infiltration was present in 6, 3 with coincident IC lesions. Four with available follow-up were treated for MCL, all with remission of GN (1 PGNMID, 2 C3 dominant GN, 1 MN). Ten patients were biopsied while MCL was in remission; these findings were attributed to various underlying diseases.

**Conclusions:** In patients with active MCL who undergo kidney biopsy, 68% had kidney biopsy findings attributable to lymphoma. Diverse immune complex diseases were seen in ~50%, including monoclonal, polyclonal, and C3 dominant GN patterns, and nearly 1/3rd had lymphomatous infiltration. Limited follow-up suggests these IC lesions respond to MCL-directed therapy.

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**PO1940**

**Anti-Brush Border Antibody Disease with Nephrotic Syndrome: A Clinicopathologic Analysis of Five Cases**

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**Background:** Anti-brush border antibody (ABBA) disease is a recently described etiology of acute kidney injury and progressive renal tubular injury that mainly affects the older patients. ABBA is characterized by the presence of circulating autoantibodies to proximal tubular brush border protein LRPII(megalin) and IgG immune complex deposits along the basement membrane of proximal tubules. In the present study, we report 5 cases of ABBA that all presented as nephrotic proteinuria.

**Methods:** We retrospectively screened for ABBA disease through our renal biopsy cohort from January 2018 to May 2021. The anti-brush border antibody disease was diagnosed based on the presence of ABBA in the serum, showing positive ABBA on a kidney section by indirect immunofluorescence with patient’s serum, and kidney histology. Histology of the biopsies and clinical data were analyzed. Serologies, including ANA, dsDNA, ANCA, anti-GBM were negative. C3 and C4 levels were normal. Neither acute tubular injury nor intensive Interstitial inflammation were found in all these biopsies. Proximal tubular brush border and glomerular basement membranes stained positive for IgG in all cases, and 3 cases also have positive deposits in some segments of TBM. Staining for IgG subclass showed that IgG1 was positive, while IgG2, IgG3 and IgG4 were not detected. Interestingly, we found light chain monoclonal of lambda in two patients. Electron microscopy showed diffuse podocyte foot process effacement in all cases. All patients received prednisone plus cyclophosphamide therapy and achieved complete recovery after 2 months (range: 1-3) (Table 1).

**Conclusions:** We report 5 cases of anti-ABBA disease with nephrotic syndrome recovered after treatment with prednisone and cyclophosphamide. The mechanism of podocyte injury in anti-ABBA disease requires additional studies.
Neutralizing Antibodies in Preventing Polyomavirus Nephropathy: Lessons from the Mouse

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Background: Definitive polyomavirus nephropathy (PyVN) affects kidney transplants and impacts allograft function and survival. Data suggest that neutralizing PyV strain-specific antibodies can attenuate and possibly even prevent disease. Here we report observations from the mouse on the protective role of anti-PyV antibodies.

Methods: Six breeding mice had been exposed to murine PyV (MUPyV). They had developed a robust IgG response while lacking definitive PyV and only showing minor qPCR evidence of intra organ MUPyV. Newborns of exposed breeders were split: group 1 (n=23) was injected at birth with MUPyV; group 2 (n=19) was not injected. Group 3 (n=24) was born to unexposed breeders and injected with MUPyV at birth. Tissue, plasma, and urine were analyzed at various time-points (0,1,2,3,6, and 10 weeks) by light microscopy, immunohistochemistry, qPCR, and MUPyV antibody titer testing. The nonparametric Wilcoxon Rank Sums test was used for p-value comparisons.

Results: Newborns from exposed breeders had IgG titers between 160-640, no IgM, and only subclinical minor molecular evidence of intra organ MUPyV by qPCR. During 10 weeks of follow up, groups 1 and 2 both cleared MUPyV. By week 10, MUPyV was largely undetectable in the setting of significantly reduced IgG titers (0-40; no IgM). Prior to clearance, both groups displayed a mild transient increase in IgG titers (up to 2560; no IgM) at weeks 2 and 3. MUPyV clearance occurred earlier in group 2 with significantly lower qPCR reads in kidney and spleen noted on week 2 (P<0.03). There was no MUPyV induced organ injury. In contrast, group 3 showed persistently high intra organ qPCR reads starting post MUPyV injection on day 0 and lasting through week 10 (p<0.05 compared to groups 1/2). Histologically apparent viral tissue injury was first noticeable at week 1 and persisted thereafter. IgG and IgM levels remained undetectable until week 2, when they began to slowly rise. By week 10, IgG titers had risen significantly (up to 20480) while IgM titers had decreased to 0.

Conclusions: Preexisting neutralizing antibodies protect from PyVn and facilitate clearance of subclinical MUPyV. In contrast, established MUPyV induced disease/injury is unaffected by neutralizing antibodies. This data can help in developing preventative treatment strategies in man.
Insidious Granulomatous Interstitial Nephritis (GIN) in a Patient with a History of Diffuse Large B Cell Lymphoma (DLBCL)

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Introduction: GIN has diverse etiology as infections, vasculitis, sarcoidosis, and lymphoma. These diseases can occur in the same patient, making diagnosis and treatment decisions challenging. Here, we report a case of GIN with a fever that developed after a long period since the complete remission (CR) of DLBCL.

Case Description: A 46-year-old man was admitted to our hospital with malaise, dyspnea, and severe renal failure (RF). Twenty years before the admission, he was diagnosed with DLBCL. After 4 years of treatments, he achieved CR. Thirteen years after CR, he presented to our hospital with a persistent fever. At this time, impaired renal function (serum Cr 1.8 mg/dL) was noted. FDG-PET CT showed uptake in the enlarged lymph nodes (LN) around the pancreas and in both kidneys. Biopsy of the LN revealed multiple epithelioid granulomas and no evidence of recurrence of DLBCL, and his fever was resolved spontaneously. Two years later, he was admitted due to advanced RF (serum Cr 11.8 mg/dL) and hemodialysis (HD) was initiated. Both kidneys were atrophic on CT scan, whereas they still showed intense uptake on Ga scintigraphy. The renal biopsy showed diffuse GIN, but recurrence of DLBCL, sarcoidosis, and vasculitis was denied. Examinations for Tuberculosis (TB) were only positive for the interferon-gamma release assays (IGRAs) and negative for renal stains, systemic cultures, and image studies for lung TB. Anti-TB therapy was administered for his persistent fever that recurred after hospitalization. After the initiation of the anti-TB treatment, his fever gradually resolved, and he has been well, although he cannot withdraw HD.

Discussion: The course of our case suggests that the GIN was induced by TB infection, although our patient did not show typical features of systemic TB except for positive IGRA. There has been an increase in the number of cases of TB infection diagnosed following GIN, which is presented not with the typical features of classical renal TB but with a more insidious form (Oliveria et al., Clin Kidney J 2017). These cases are often diagnosed later and may associate with a poor prognosis. Our case suggests that anti-TB therapy should be considered for patients with IGRA-positive GIN after excluding other etiologies of GIN, even without the other diagnostic evidence of systemic TB.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

598
PO1949

A Case of Asymptomatic Juxtaglomerular Cell Tumor (JGCT)
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Introduction: JGCT/ reninoma is an extremely rare benign neoplasm of kidneys typically manifesting as hypertension and hypokalemia secondary to renin secreting tumor cells. We present a case of JGCT presenting as an asymptomatic renal mass.

Case Description: A 61-year-old male of with diabetes mellitus, hypertension (>15 years duration, well-controlled with Losartan 100mg daily) presented with right upper quadrant abdominal pain. Computed tomography scan of abdomen/pelvis with intravenous contrast revealed cholelithiasis without cholecystitis and an incidental 3cm mass at the mid-pole of the left kidney without renal vascular involvement. Kidney ultrasound 5 years prior did not show any renal mass. Spot urinalysis showed no hematuria and proteinuria was 96 mg/g (normal < 150 mg/g). Baseline serum creatinine was 1.3-1.4 mg/dl (normal 0.7-1.3 mg/dl). 24-hour urine creatinine clearance was normal. Given the high suspicion for a malignancy, the patient underwent recommended left radical nephrectomy. Kidney mass biopsy diagnosed JGCT. Light microscopy showed well circumscribed tumor with glomoid appearance with sheets of uniform round- to-polynuclear cell with clear to eosinophilic cytoplasm. In addition, there were focal endocrine-like, marked atypical hyperchromatic nuclei occasionally scattered throughout the tumor. Immunohistochemical stains demonstrated diffuse positivity in tumor cells for CD34 (Figure 1), CD117 and vimentin (Figure 2). Patient sustained a slight rise in creatinine post nephrectomy as expected and he continued to require only one anti-hypertensive medication. Patient remained in remission with stable kidney function without recurrence of tumor at 2 years follow-up.

Discussion: JGCT can present as hypertension and hypokalemia. Our patient had optimal blood pressure control on monotherapy. Losartan may have masked the associated hypokalemia. Nephrectomy (partial or radical) is curative and is the recommended treatment.

CD 34 stain and vimentin stain kidney mass pathology images

PO1950

Disseminated Histoplasmosis Mimicking Crohn Disease in Kidney Transplant Recipient
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Introduction: Fungal infections can occur after a kidney transplant due to the use of immunosuppressants. Histoplasmosis is an endemic infection in Mexico and it’s pulmonary phase is very common. The risk of complications is high, so an early diagnosis should ideally be made with a biopsy of the affected tissue. We report the case of a kidney transplant recipient with chronic diarrhea associated with disseminated histoplasmosis simulating Chrohn’s disease.

Case Description: A 50-year-old woman with history of CKD of unknown etiology underwent living donor kidney transplant. She received induction with basiliximab and maintenance therapy based on Sirolimus and mycophenolate mofetil. One year after transplantation, she was evaluated for fever and pulmonary nodules, without detecting infectious etiology. One year later, she presented diarrhea and based on the presence of colonic ulcers, Chrohn’s disease was suspected and treatment with mesalazine was started. Due to the persistence of diarrhea, a second coloscopy was performed establishing the diagnosis of histoplasmosis by means of biopsies of the colonic mucosa and with urinary antigen. Itraconazole B treatment was initiated and 2 weeks later urinary antigen was negative and renal function returned to baseline. Itraconazole-based maintenance therapy was chosen.

Discussion: Acute pulmonary histoplasmosis is caused by inhaling spores and it tends to be a self-limited disease. Disseminated histoplasmosis is common in immunocompromised patients. Gastrointestinal involvement is clinically manifested in 20% of cases, although urinary antigen has a 95% specificity, histopathological identification with PAS(-) and Giemsa(-) stains, remains the ideal test, as they showed submucosal and lamina propria macrophage invasion at the intestinal tissue. Chronic diarrhea can be a manifestation of systemic fungal infection in kidney transplant recipients.
PO1952

Diuretic Use, Comorbidity, and Length of Stay in Pediatric AKI

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Background: Acute kidney injury (AKI) and fluid overload (FO) both have well known negative effects on morbidity and mortality in many populations. The combination of AKI and FO is associated with synergistically worse outcomes in critically ill children. Diuretic use in management of AKI and FO has been studied in adults with widely varied outcomes ranging from improved mortality to no significant change to increased comorbidity such as prolonged mechanical ventilation. Therefore utility of diuretics remains unclear, and their use in pediatric patients with AKI has not been characterized.

Methods: The Pediatric Hospital Information System (PHIS) database was queried for patients with diagnosis of AKI from January 2015 to December 2019 with admission LOS <15 days. Those <1 or >18 years of age were excluded. ICD codes were used to discern complex chronic conditions (CCCs) as well as acute comorbidities. Duly medication exposure was used to determine diuretic use. LOS in both the ICU and the inpatient floor was assessed. CCCs of interest were chronic kidney disease (CKD), kidney transplant, and heart failure. Measured comorbidities included: shock, mechanical ventilation, hypoxemia, fluid overload, ascites, edema, and oligoanuria. Numeric data were summarized as medians and IQRs and categorical data as frequency and percent. Associations between diuretic use and comorbidity was assessed by Wilcoxon’s rank-sum test and Fisher’s exact test. Length of stay was then assessed by longitudinal regression.

Results: There were 5490 encounters for analysis with diuretic use in 951. Demographics were similar between groups. Those with CKD or heart failure were more likely to receive diuretics, while those with transplant status were less likely to receive diuretics. LOS was 1.67 days longer in those who received diuretics despite adjustment for age, gender, and illness severity including CCCs. All acute comorbidities were increased in those who received diuretics.

Conclusions: Children with underlying CCCs were more likely to receive diuretics and to have longer LOS. Comorbidities and LOS were also increased in children with AKI who received diuretics regardless of disease severity. This is clinically important as diuretic use may be correlative for worse outcomes and increased costs. Due to database limitations, temporal association is unknown and further study is needed.

PO1954

Neonatal AKI Is Associated with Impaired Renal Function at 24 Months of Age

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Background: Neonatal acute kidney injury (nAKI) is common, occurring in up to 30% of neonatal intensive care admissions. However, there are currently no guidelines for nephrologic evaluation after the neonatal period. Our objective was to determine the incidence of renal dysfunction at 24-months of age and to identify associated risk factors following nAKI.

Methods: Retrospective single-center cohort study of infants with nAKI (defined as rise in creatinine (Cr) ≥ 0.3, abnormal initial Cr for gestational age, or abnormal rate of Cr decline) seen in pediatric nephrology clinic at 24-months. Abnormal estimated glomerular filtration rate (eGFR) (< 90 ml/min/1.73m²), hypertension (BP ≥ 95th%ile), proteinuria (TPC ≥ 0.5), and renal length (≥ 5th%ile) were correlated with high risk NICU events and exposures. Data was obtained by chart review. eGFR was calculated using cystatin C and creatinine separately, using the CKID cystatin C and the revised Schwartz equations, respectively. Data was analyzed using t-tests, Wilcoxon Rank Sum Test, or Chi-square as appropriate.

Results: 36/42 infants with history of nAKI referred to nephrology had a 24-month visit. 20 of 36 subjects (55.5%) had at least one renal abnormality, with 14 (39%) having eGFR < 90 ml/min/1.73m² by cystatin C, 7/36 (19.4%) had proteinuria, 3/36 (8.3%) had hypertension, and 4/36 (11.1%) had abnormal renal length. 1/15 subjects with reduced GFR by cystatin C also had a reduced eGFR by serum creatinine. Subjects with renal dysfunction at 24 months had a neonatal history of more vasopressors exposure days (mean, 4.5 vs 0.25, p = 0.002), more total diuretic days (mean 122 vs 51 p=0.03), were more likely to have a diuretic at discharge (n=11 vs n=3, p = 0.026), or to be of extremely low birth weight (ELBW < 1000 g) (n=14 vs n=4, p = 0.007) compared to those without renal dysfunction.

Conclusions: The majority of children with nAKI had evidence of renal dysfunction at 24-month of age. Serum Cystatin C was more sensitive at identifying kidney dysfunction than Cr. All children with nAKI should be referred for renal follow-up with a particular focus on children who were ELBW, required vasopressors, or had prolonged diuretic use in the neonatal period.

PO1955

Kidney Outcomes Among Extremely Preterm Born Adolescents with Neonatal AKI

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Background: Infants born preterm are at increased risk for neonatal acute kidney injury (nAKI). AKI increases the risk for CKD long term however, long term kidney outcomes among preterm born survivors of nAKI are not well known. The aim of the study is to evaluate associations between nAKI and microalbuminuria, elevated blood pressure (BP), and reduced kidney mass in adolescents born extremely preterm.

Methods: We obtained 2 manual BP’s, a random urinalysis, and kidney ultrasound on adolescents of the University of North Carolina ELGAN (Extremely Low Gestational Age Newborn) cohort between 2017-2019. We retrospectively obtained serum creatinine (Cr) studies from the initial neonatal intensive care unit hospitalization between 2002-2004. We defined nAKI by neonatal KDIGO guidelines.

Results: Of the 31 participants born <28 weeks gestation, mean age was 15.2 years and 58% were overweight/obese. 32% of adolescents had elevated BP, 13% had reduced kidney mass, and 13% microalbuminuria. 52% of the adolescents had a history of nAKI. 81% experienced Stage 1 AKI, 19% had Stage 2 AKI, and no participants experienced Stage 3 AKI. Those with nAKI had lower birth weight, lower APGAR scores, more mechanical ventilator days, lower urine output, greater vasopressor exposure, greater indomethacin exposure, less methylxanthine exposure, greater # of serum SCr measurements, and more days in the hospital. During adolescence, those with nAKI had lower frequency of elevated BP and microalbuminuria but greater frequency of reduced kidney mass (Table 1).

Conclusions: Adolescents with a history of nAKI were more frequently exposed to nephrotoxic factors and had more indicators of severe illness in early life. However, nAKI was not significantly associated with elevated BP, microalbuminuria, or kidney mass in this sample of adolescents born extremely preterm. Further follow up is needed to better characterize manifestation of CKD in adolescents after nAKI.
Prediction Model of CKD at the Age of One Year Following Prenatal Severe Urinary Tract Dilation

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Background: Early childhood chronic kidney disease (CKD) has a wide spectrum of health and developmental implications. Renal replacement therapy may be needed during childhood. Prenatal counselling regarding future renal outcome in cases presenting prenatally with severe urinary tract dilation (UTD) is challenging. We aimed to create a prenatal ultrasound model for the prediction of early childhood CKD following fetal severe UTD.

Methods: A retrospective cohort study was conducted in a national referral centre. Fetuses diagnosed with severe UTD and maintained follow up comprised the study group. The main outcome was CKD at the age of one year. Logistic regression analysis was used to identify prognostic prenatal ultrasound variables for the renal outcome. Analysis of Maximum Likelihood Estimates was performed to create a multivariable predictive model.

Results: 87 fetuses comprised the study group. 15 cases (17.2%) developed CKD by the age of one year. In all, renal dysfunction and renal dysplasia were diagnosed at birth. Post-natal diagnoses were lower urinary tract obstruction in 5 cases, vesical-ureteral reflux in 10 cases. Bilateral hydrourephosis, abnormal bladder, hydronephrosis, normal kidney function, and abnormal parenchyma, were all significantly related to CKD at the age of one year. A combination of prenatal ultrasound variables yielded a model with a discriminatory ability of c=0.976.

Conclusions: A prediction model incorporating prenatal ultrasound features can discriminate between a normal and an impaired renal outcome at the age of one year. These sonographic features are related to the extent of renal dysplasia and to the remaining functioning nephron mass. Data presented may be used to develop more effective risk assessments and customized parent counseling.

Association of Antenatal Corticosteroids with Later Kidney Function in Adolescents Born Preterm with Very Low Birth Weight

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Background: Antenatal corticosteroids (ANCS) are given to pregnant women who are at risk of preterm delivery to accelerate fetal lung development. While studies in sheep suggest that ANCS program deleterious effects on renal development leading to higher blood pressure (BP) and worse kidney function, the persistent effects of ANCS exposure on the long-term health of at-risk individuals remains undescribed. We investigated the association of ANCS with BP and kidney function in adolescents born preterm and hypothesized that ANCS are associated with worse BP and kidney function.

Methods: This was a long-term prospective birth cohort of 175 14-year-old adolescents born preterm with very low birth weight (VLBW, <1500 g). We measured manual BP, serum creatinine, and first-morning urine albumin-to-creatinine ratio (ACR), defined high BP as a ≥120/80 mmHg and albuminuria as ACR >30 mg/g, and calculated the estimated glomerular filtration rate (eGFR). We used generalized linear models to estimate the association of ANCS with the outcomes.

Results: The cohort consisted of 58% non-Black participants, 55% female participants, and 53% were exposed to ANCS. Among all participants, mean systolic BP was 106.4 mmHg, 13% had high BP, median eGFR was 124.9 ml/min/1.73 m² (n=123), and 7% had albuminuria (n=134). In unadjusted analyses, ANCS was not associated with high BP (RR 1.08 mmHg, 95% CI 0.49–2.37), eGFR (β 3.74 ml/min/1.73 m², 95% CI -6.74 to 14.22), or albuminuria (RR 1.31, 95% CI 0.34–5.01).

Conclusions: Our research findings indicate that ANCS exposure was not associated with compromised kidney function or worse BP in adolescents born preterm with VLBW. Future analyses will include adjusting for potentially confounding factors in multivariable models and continuing to assess participants’ long-term BP and kidney function.

Predictors of Renal Function in Pediatric Liver Transplant Recipients


Background: Impaired kidney function is a well-recognized complication following liver transplant (LT). In adult LT recipients, the cumulative incidence of renal insufficiency is as high as 10% in 10 years. The burden of kidney dysfunction is thought to be higher in pediatric LT recipients due to longer exposure to nephrotoxic agents & longer lifespan. The aim of this study is to identify predictors of renal function decline in pediatric LT recipients.

Methods: This is a retrospective study of pediatric LT recipients between June 2008 to November 2014. Clinical and biochemical characteristics and eGFR were obtained at baseline, 6, 12, 24, and 60 months. CKD was defined as an eGFR <60 ml/min/1.73 m² for a least 3 months post-LT. A Multivariable Cox Proportional Hazards model was created to determine predictors of progression to CKD post-LT.

Results: Table 1 shows the baseline characteristics of patients with CKD post-LT compared to those who did not. In bivariate analysis, age, African American race, tumor diagnosis, baseline eGFR, pre-transplant HD and AKI were associated with progression.

Table 1

<table>
<thead>
<tr>
<th>With Normal ARI (n=58)</th>
<th>Without Normal ARI (n=52)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
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<tr>
<td>Gender</td>
<td>Male</td>
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<tr>
<td>Race</td>
<td>White</td>
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<tr>
<td>Diagnosis</td>
<td>Liver failure</td>
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Urine output in the first 12 hours of life;

**Renal hypoplasia defined by body surface area related total kidney volume below the 10th percentile of normative TKV/BSA [1, 2]
to CKD (Figure 1). In multivariable analysis, factors associated with increased risk of progression to CKD included: older age at LT (HR 1.012, p=0.001), tumor diagnosis (HR 3.602, p=0.0126) and lower baseline eGFR (HR 0.986, p=0.0014).

Conclusions: In our study we found that risk factors for CKD include: older age at the time of LT, lower baseline eGFR and tumor diagnosis. Further studies are underway to evaluate the role of Tacrolimus in the progression to CKD post LT.

Funding: Other NIH Support - This research was supported by NIH National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881

Methods: We performed a retrospective analysis of children who underwent m-TPE using the TPE 2000 filter membrane set with Prismaflex machines at our center during last year. We included children who required heparin, or bivalirudin as anticoagulation, and FFP as replacements. Given the minimum blood flow requirements of 100 ml/min, we only performed this procedure with children <10 kg who were on ECMO. To prevent hypocalcemia, we administered calcium chloride drip with starting dose of 20 mg/kg/hour before initiation of TPE. We adjusted the calcium chloride drip based on the ionized calcium monitoring scale. Additional calcium boluses were given for hypocalcemia persisting after drip adjustment to a maximum rate of 50 mg/kg/hr.

Results: We included eight children in the analysis who required both CRRT and TPE. The age range was 23 days–15 years (median: 2 years). On average, we performed 3.1 treatments per patient with a mean treatment time of 175 minutes. In 2/8 patients, bivalirudin was used. Common complications included hypocalcemia requiring additional calcium bolus (2/8), high transmembrane pressure (TMP) (1/8), and hemodynamic instability (1/8). There was no significant correlation between age and dose of calcium drip required (p-value: 0.433); and ECMO and requirement of additional calcium boluses (p-value: 0.107). There was a significant improvement in inflammatory markers (D-dimer, CRP, IL6) and bilirubin level post-pheresis treatment.

Conclusions: The TPE procedure using Prismaflex may be a practical option for children undergoing CRRT, but further studies are required to assess its use in children with weights less than 20 kg. Most children tolerated the procedure well in our study. Hypocalcemia is a critical complication with this procedure.

PO1961

NT-ProBNP a Potential Biomarker for Assessing Volume Status of Patients Receiving CRRT


Introduction: Fluid overload is a significant risk factor for morbidity and mortality in patients receiving CRRT. Records of fluid balance, clinical signs of fluid overload (weight, peripheral edema), hemodynamic parameters (tachycardia, blood pressure), filling pressure (CVP), bioelectrical impedance, and radiological studies (CXR, IVC diameter) are the clinical tools that are commonly utilized to help assess volume status, each of which has their own limitations. The aminoterminal fragment of B-type natriuretic peptide (NTproBNP), a biomarker for left ventricular myocardium, is well established as a good diagnostic and prognostic indicator of heart failure. Our previous observation of a correlation of NTproBNP with volume status in infants without cardiac disease who received CRRT led us to use NTproBNP as a surrogate marker of volume status in a newborn currently receiving prolonged CRRT.

Case Description: NTproBNP levels were measured at least twice a week in a 4-month-old (gestational status vs postnatal age 27+4/40 weeks) infant undergoing CRRT (clearance 30–35 ml/kg/hr). NTproBNP levels were correlated with weight (used as surrogate for volume status), and clinical evidence of cardiorespiratory compromise.
PO1962
Prophylactic PD Catheter Placement for Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass: Systematic Review with Meta-Analysis
Emma H. Ulrich,1 Prabhjot K. Bedi,1 Rashid Aloobaidi,1 Catherine Morgan,1 Mike Paulden,2 Michael Zappitelli,1 Sean M. Bagshaw.
1University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; 2University of Manitoba, Winnipeg, Winnipeg, MB, Canada.

Background: Infants undergoing cardiopulmonary bypass (CPB) are at high risk of fluid overload, requiring peritoneal dialysis (PD). This systematic review evaluates whether prophylactic PD catheter (PDC) insertion at the time of cardiac surgery improves post-operative outcomes.

Methods: Comprehensive literature search was completed Oct-2020. We identified studies that compared children ≤18 years undergoing cardiac surgery with CPB and receiving prophylactic PDC (inserted intraoperatively or ≤24 hours postoperatively) vs. children who do not undergo prophylactic PDC placement. Data was extracted on population characteristics; perioperative variables; and short-term postoperative outcomes, including time to negative fluid balance (FB); presence and degree of fluid overload; duration of inotropic support and mechanical ventilation; hospital length of stay; and mortality.

Results: Of 1067 studies, 208 underwent full-text review for eligibility, and 15 were included: 4 randomized controlled trials; 9 cohort studies; and 2 case-control studies. Intervention was prophylactic PDC insertion with passive peritoneal drainage in 6; PD in 7; and passive peritoneal drainage or PD in 2. The comparator group typically received furosemide. Baseline characteristics were heterogeneous for the included studies with respect to age, weight, and illness severity. Surgical procedures performed were also variable within and between studies. Time to negative FB and prevention of fluid overload showed mixed results with some studies favoring prophylactic PDC and others showing no difference. Pooled unadjusted OR for in-hospital mortality was 0.75 (95% CI: 0.05-11.11) (Figure 1). No studies reported serious PDC-related complications. Risk of bias was high in most studies, due to higher illness severity in the intervention groups, small sample size, and observational nature of studies.

Conclusions: Prophylactic PDC insertion is relatively safe in children undergoing cardiac surgery with CPB. Some studies have shown prophylactic PDC improves post-operative outcomes, including time to negative FB and in-hospital mortality; others have shown no difference.

PO1963
Iodine-Induced Hypothyroidism in Pediatric Patients Receiving Peritoneal Dialysis: Is Risk Mitigation Possible?
Sai Sudha Mannemuddu,1,2 Heather Morgans,3 Bradley A. Warady.
1East Tennessee Children’s Hospital, Knoxville, TN; 2The University of Tennessee Health Science Center College of Medicine, Memphis, TN; 3Children’s Mercy Hospitals and Clinics, Kansas City, MO.

Background: Children with end-stage kidney disease who receive chronic peritoneal dialysis (PD) are at increased risk for thyroid dysfunction. Iodine-induced hypothyroidism (IIH) from exposure to iodine-containing agents is poorly appreciated, particularly in infants and small children.

Methods: An international survey was conducted to better understand current practices pertaining to iodine exposure and the frequency of IIH in patients receiving PD, and to assess awareness of this issue amongst pediatric nephrologists.

Results: 89 centers responded to the survey. Hypothyroidism in PD patients was diagnosed in 64% of responding centers, although only 1/3 of centers suspected/diagnosed IIH. Etiologies of IIH included exposure to iodine-containing PD caps (53%), cleaning solutions with iodine (37%), and iodinated contrast (10%). While the majority of centers (58%) routinely evaluate thyroid function, only 34% aimed to limit iodine exposure by avoidance of iodine-containing cleaning solutions (73%) and contrast agents (33%), monitoring of initial PD drain volume (30%), and use of a non-iodine PD cap (23%). Of centers not routinely evaluating for or utilizing methods to prevent IIH, 81% reported being unaware of the risk.

Conclusions: Hypothyroidism is diagnosed in a substantial percentage of pediatric PD programs. Education pertaining to the risk of IIH associated with iodine exposure may decrease the incidence.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1964
Factors Associated with High-Cost Hospitalizations for Hemodialysis Catheter-Associated Blood Stream Infections in Children
Heather L. Wasiak,1 Alicia Neu,2 Bradley A. Warady,1 Brendan Crawford,3 Troy Richardson,4 Heidi G. De Souza,5 Diana Cardwell,1 Rebecca Ruebner.2
The Standardized Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) collaborative State University of New York Upstate Medical University, Syracuse, NY; 1Johns Hopkins University, Baltimore, MD; 2Children’s Mercy Hospitals and Clinics, Kansas City, MO; 3Children’s Health Children’s Medical Center Dallas, Dallas, TX; 4University of Arkansas for Medical Sciences, Little Rock, AR; 5Children’s Hospital Association, Overland Park, KS.

Background: Hospitalizations of adults for hemodialysis catheter-associated blood stream infections (HD-BSI) lead to high costs. No studies have evaluated hospitalization costs for HD-BSI in children or identified factors associated with high-costs.

Methods: The Standardized Care to Improve Outcomes in Pediatric End-Stage Kidney Disease (SCOPE) collaborative database was used to identify HD-BSI. SCOPE database linked to the Pediatric Health Information Systems (PHIS) database which provided hospitalization billing data. High-cost hospitalization defined as cost above 50th percentile in our study population. Multivariable logistic regression used to assess the relationship between high-cost hospitalization and patient and clinical characteristics.

Results: The median(IQR) LOS for HD-BSI hospitalization was 3(3-10) days. The median(IQR) cost for HD-BSI hospitalization was $18,375($11,584-$36,266). Cost for each service line was higher in high-cost group(p<0.001) (Figure 1). High-cost HD-BSI hospitalization was associated with ICU stay, LOS, need for catheter replacement/rewiring (Table 1). ICU stay (aOR=4.84, 95% CI 1.66-14.08, p=0.004) and need for catheter procedure (aOR 6.29, 95% CI 2.76-14.35, p<0.001) remained associated with high-cost hospitalization in a multivariable model.

Conclusions: Hospitalizations of children for HD-BSI lead to high costs. Efforts to prevent HD-BSI may reduce the costs of caring for children on hemodialysis.

Figure 1

Table 1

POI1965
Hemoglobin and Mortality Across Race Among Children Who Transferred to Dialysis Therapy: An Analysis of CEFDIM and USRDS Data
Michael Tronske,1 Marciana Laster,2 Jui-Ting Hsiung,1 Kamyar Kalantar-Zadeh,1 Elani Streja.1 1University of California Irvine, Irvine, CA; 2University of California Los Angeles, Los Angeles, CA.

Background: Low hemoglobin (Hgb) is a strong predictor for mortality in adult dialysis patients, and children on dialysis experience optimal Hgb levels less frequently than adults. Racial disparities have also been identified in pediatric dialysis patients, with Blacks experiencing unfavorable clinical outcomes and poor access compared to Whites. However, there is less literature examining the impact of race on the association of Hgb with mortality among pediatric patients on dialysis.

Methods: We retrospectively studied two cohorts of children (age <21) using data from a large dialysis organization (CEFDIM) and a national data system (USRDS). CEFDIM (n=1069) were followed from 2006-2011, while USRDS (n=26,254) were followed from 1995-2016. The association between Hgb and mortality was observed using Cox regression analyses stratified by race, categorizing Hgb by g/dL as well as z scores (ref: Hgb 11-12 g/dL, z scores -0.5 to 0.5). Covariates considered in the models included age, sex, BMI, albumin, comorbidities, and dialysis modality type.

Results: Among Black CEFDIM patients, Hgb <10 g/dL was associated with increased mortality (7.9 [0.97,65.27]), as was Hgb z scores <-1.5 (8.62 [1.92,38.77]). Among White CEFDIM patients, these associations were null, and no deaths occurred for z scores <-1.5. Among Black USRDS patients, Hgb above 12 g/dL appears to be protective (0.83 [0.65,1.06]), which was not a protective range for White patients. Meanwhile z scores <-1.5 were significantly protective among White patients (0.82 [0.70,0.96]), but not among Black patients (0.94 [0.79,1.13]).

Conclusions: In children undergoing dialysis, protective Hgb target ranges appear to differ by race, with White children experiencing lower mortality risk from extremely low values and Black children receiving protection from high values.

POI1966
Children on Chronic Hemodialysis Before the First Year of Age: A Three-Year Survival Analysis
Cristina Henrique,2 Arnaldo Roizenblat,1 Maria fernanda C. Carvalho,2 Fabio A. Takih,1 Paulo C. Koch Nogueira.1 1Universidade Federal de Sao Paulo, Sao Paulo, Brazil; 2Hospital Samaritano de Sao Paulo, Sao Paulo, Brazil.

Background: Peritoneal dialysis is the method of choice for infants who need renal replacement therapy (RRT). However, when it is not possible to perform it or becomes ineffective, hemodialysis is a feasible method in young children. There are few reports on the survival rate of children undergoing hemodialysis in the first year of life. The goal of this study was to determine the mortality rate and its risk factors in children starting hemodialysis during their first year of life.

Methods: We retrospectively studied two cohorts of children (age <21) using data from a reference Dialysis Center in Sao Paulo city. Data from 47 (8 females) children who underwent chronic hemodialysis before the first year of age were analyzed. Survival was characterized using Kaplan-Meier methods and log-rank tests, followed by a multivariable Cox regression model.

Results: The median weight on the first hemodialysis session was 4.3 Kg (IQR=3.4 to 5.3), while median age was 4.1 months (IQR=2.3 to 6.0), with 21 children younger than 1 month, and only one older than 6 months. Patients were categorized according to the etiology of Chronic Kidney Disease (CKD), congenital anomalies of the kidneys and urinary tract: We retrospectively studied two cohorts of children categorization according to the etiology of Chronic Kidney Disease (CKD), congenital anomalies of the kidneys and urinary tract (53.2%) was the most prevalent cause, followed by congenital renal dysplasia (23.4%), autosomal recessive polycystic kidney disease (8.5%), and other etiologies (14.9%). The survival rates were 93%, 75%, and 64% at 1, 2, and 3 years, respectively. Only cardiovascular comorbidity was significantly associated with the
decrease naso-end artery disease, 95%CI 1.7 – 19.6, p=0.006. Anuria had a significant impact on survival only in univariate analysis. Parameters such as gender, age at hemodialysis onset, ethnicity, early dialysis, etiology of CKD had no impact on survival.

Conclusions: Our retrospective cohort gathers an expressive number of children with this rare and severe condition of early onset of hemodialysis, with a uniform follow-up of all individuals. We observed satisfactory survival rates among children who started hemodialysis in their first year of life, comparable to the standards of the international pediatric dialysis centers. Hemodialysis became a safe method in young children until the performance of kidney transplantation.

POI967

The Cost-Effectiveness of Blood Product Irradiation in Pediatric Hemodialysis Patients Awaiting Kidney Transplant

Kyle Merrill, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Pediatric patients diagnosed with end-stage kidney disease often initiate hemodialysis prior to kidney transplantation. Development of anti-HLA antibodies reduces the organ pool for that patient. Blood products are one known cause of allo sensitization, or the development of anti-HLA antibodies. Gamma-irradiation of blood products may decrease this possibility. Patients with less anti-HLA antibodies have higher rates of kidney transplantation. Therefore, a cost-effectiveness analysis of whether to irradiate blood products for hemodialysis patients and the chance of successful kidney transplantation was performed.

Methods: A Markov model was utilized in this analysis. The model started with the choice to irradiate blood or not to prior to entering the Markov. To simplify the model, it was assumed that transfusion with a non-irradiated blood product will result in a CPRA of 30%. If irradiation decreased this to 10%, Patients only received one blood product exposure. After kidney transplant, it was assumed there was no graft failure and return to dialysis. Mortality rates were calculated based on age-specific mortality tables along with the annual excess mortality for each state of the patient.

Results: The irradiation strategy dominates in the base case and is both cheaper at $985,749 (versus $1,049,614) and more effective at 13.00 adjusted life years (versus 12.81) when compared to the choice of non-irradiation. A one-way sensitivity analysis was completed on the relative transplant rate and showed that a rate of 1.006 was the breakpoint where irradiate dominates non-irradiate. A one-way analysis on the cost of blood product irradiation found that even if irradiation costed 100% of the base case, it was still the dominating choice. The last one-way sensitivity analysis noted that as the monthly cost increased from $0 to $10,000 per month, that until the monthly cost was around $3,700, then the more cost-effective choice was to not irradiate, but at any cost higher than $3,750, then the choice to irradiate dominate non-irradiation.

Conclusions: Blood product irradiation was found to be more cost effective. Even with a slight increase in transplant rate, irradiate remained the more cost-effective choice. The cost of irradiation does not affect the choice to irradiate but if hemodialysis were cheaper, the choice to not irradiate was more cost-effective.

POI968

Partial Extracorporeal Circuit Blood Primers Are Safe and Do Not Decrease Hematocrit in Small Children

Michaela Collins, Xavier French, Kelli A. Krallman, Stuart Goldstein, Jean-Philippe Roy, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Partial blood primes (PBP) for extracorporeal therapies have the potential to decrease unique number of blood unit exposures in children when compared to full blood primes (FBP). Pediatric patients (pts) receive a blood prime when the extracorporeal circuit volume (ECV) exceeds 10-15% of their total blood volume (TBV). FBP is collected red blood cells (PRBC; Hct 60%) for the entire ECV while PBP utilizes a standardized approach for less PRBC volume per circuit, allowing the same unit to be used for 3-12 treatments depending on ECV. We aimed to show that PBP does not result in more hemodilution or need for transfusions compared to FBP.

Results: Data from pts receiving continuous kidney replacement therapy (CRRT) or intermittent therapies (INT), including hemodialysis, plasma exchange and apheresis, with FBP were collected retrospectively whereas data from PBP were collected prospectively beginning 8/2019 after a change in local practice. The primary outcomes were 1) pre- and post-treatment hematocrit (Hct) and 2) number of transfusions required between FBP and PBP.

Conclusions: The use of PBP does not result in hemodilution compared to FBP, nor does it result in the need for more transfusions. PBP is a safe alternative to FBP, it improves blood product stewardship and has the potential to reduce sensitization in children with ESKD or at risk for CKD, which may facilitate kidney transplant.

Table 1. Factors associated with re-hospitalization in the first year

<table>
<thead>
<tr>
<th>Age at Transplant</th>
<th>Adjusted HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>1.21 (1.12-1.39)</td>
</tr>
<tr>
<td>6-10</td>
<td>Ref</td>
</tr>
<tr>
<td>11-17</td>
<td>1.01 (0.9-1.12)</td>
</tr>
<tr>
<td>18-21</td>
<td>1.11 (0.96-1.30)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>1.00 (0.96-1.17)</td>
</tr>
<tr>
<td>Other</td>
<td>1.31 (1.01-1.68)</td>
</tr>
<tr>
<td>Other</td>
<td>1.17 (0.99-1.37)</td>
</tr>
<tr>
<td>Insurance Type</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>1.22 (1.03-1.43)</td>
</tr>
<tr>
<td>Public</td>
<td>0.74 (0.46-1.17)</td>
</tr>
<tr>
<td>Center Volume (transplants/year)</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.19 (0.92-1.56)</td>
</tr>
<tr>
<td>5-10</td>
<td>1.26 (1.12-1.49)</td>
</tr>
<tr>
<td>10-15</td>
<td>1.16 (1.00-1.36)</td>
</tr>
<tr>
<td>16-19</td>
<td>1.28 (1.03-1.59)</td>
</tr>
<tr>
<td>20-30</td>
<td>1.30 (1.14-1.48)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.66 (1.50-1.84)</td>
</tr>
</tbody>
</table>

*p≤0.05

Table 1. Het Levels and Change by Blood Prime Type (all values mean (SD))

<table>
<thead>
<tr>
<th>Pre-Transplant Hct (%)</th>
<th>Post-Transplant Hct (%)</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBP</td>
<td>33% (6.3%)</td>
<td>30% (5.7%)</td>
</tr>
<tr>
<td>PBP</td>
<td>33% (6.3%)</td>
<td>30% (5.7%)</td>
</tr>
</tbody>
</table>

Conclusions: The background: the burden of readmission within one year after pediatric kidney transplant (PKTx) is poorly described, with only one single center study describing rates of readmission as high as 79%. We aimed to examine the epidemiology of readmission after PKTx in a national U.S. cohort.

Methods: We linked the National Registry of Transplant Recipients (SRTR) and the Pediatric Health Information System (PHIS) database, a group of over 50 U.S. pediatric medical centers, to identify PKTx recipients <21 years old who received a kidney-only transplant from 2002-2018 and were discharged from the transplant hospitalization with a functioning graft. We characterized the epidemiology of patient demographic, clinical and transplant factors associated with the initial transplant hospitalization and readmission. We also examined risk factors for readmission within a year using multivariable Cox proportional hazard modeling.

Results: We identified 4,566 patients with a median age of 13 years, 46% had CAKUT and 45% were white, non-Hispanic. Within a year, 3,136 (69%) were readmitted. Factors associated with increased hazard of readmission were age <6 years, black race, public insurance, centers with <15 transplants/year and initial transplant admission >10 days. Transplant admission >5 days was associated with decreased hazard of readmission in the first year.

Conclusions: Over two-thirds PKTx recipients were readmitted within a year post-transplant. Readmission was associated with younger age, black race, public insurance, initial transplant hospitalization and transplant center volume. Future studies to identify modifiable risk factors associated with readmission are planned. Our findings can help improve care models to reduce healthcare utilization and cost.

Funding: NIDDK Support
PO1970

**Encouraging Outcomes from Using a Small-Donor Single Graft in Pediatric Kidney Transplantation**

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**Background:** The use of small pediatric kidneys as single for transplantation is controversial, due to the potential risk for graft thrombosis and insufficient nephron mass.

**Methods:** Aiming to test the benefits of transplanting these kidneys, 375 children who underwent kidney transplantation in a single center were evaluated: 49 (13.1%) received a single graft from a small pediatric donor (≤15Kg, SPD group), 244 (65.1%) from a bigger pediatric donor (>15Kg, BPD group) and 82 (21.9%) from adult living donors (group ALD).

**Results:** Groups had similar baseline main characteristics. After 5 years of follow-up, children from SPD group were comparable to children from BPD and ALD in patient survival (94, 96, and 98%, p=0.423); graft survival (89, 88, and 93%, p=0.426); the frequency of acute rejection (p=0.998); the incidence of post-transplant lymphoproliferative disease (p=0.671); the rates of vascular thrombosis (p=0.846) and the necessity for post-transplant surgical intervention prior to discharge (p=0.905). The longitudinal evolution of eGFR was not uniform among groups. The 5 groups presented a decrease in the eGFR, but the slope of the curve was steeper in ALD children. At 5 years, the eGFR of ALD group was 10 ml/min/1.73m² inferior to the others. At that time, the eGFR from SPD group was statistically similar to the BPD (p=0.952).

**Conclusions:** In a specialized transplant center, the use of small single pediatric donor kidneys is as successful as bigger pediatric donors or adult living donors in transplants after 5 years of follow-up.

PO1971

**Clinical Characteristics of Recurrent Focal Segmental Glomerulosclerosis (rFSGS) After Kidney Transplant (KTx) Through ComparablePhenotypic Algorithm Analyses of Multicenter Data**

Vikas R. Dharindharka,¹ Rebecca R. Scobell,² Mahmoud Kallash,³ Amy Goodwin Davies,² Nicole Marchesani,² Mitchell Maltenfort,² Leslie Walther,¹ Megan Kelton,¹ Marget Bock,¹ Eliza Blanchette,² Hillary Stone,² Caroline A. Gluck,² Frank E. Hullekes,² Leonardo V. Riella, William E. Smoyer,¹ Mark Mitsuefi,² Bradley P. Dixon,¹ Joseph T. Flynn,¹ Michael J. Somers,⁶ Christopher B. Forrest,² Susan L. Furf,² Michelle Denburg,¹ ¹ University of Washington in St Louis, St Louis, MO; ² The Children’s Hospital of Philadelphia, Philadelphia, PA; ³ Nationwide Children’s Hospital, Columbus, OH; ⁴ Seattle Children’s Hospital, Seattle, WA; ⁵ Children’s Hospital Colorado, Aurora, CO; ⁶ Boston Children’s Hospital, Boston, MA; ⁷ Massachusetts General Hospital, Boston, MA; ⁸ Nemours Biomedical Research Center for Pharmacogenomics and Translational Research, Wilmington, DE; ⁹ Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; ¹⁰ University of Colorado, Denver, CO.

**Background:** Primary FSGS, a glomerular disease, has a high rate of progression to end stage kidney failure and varying rates of recurrence after KTx. Treatment effects are harder to determine, due to high multicenter populations and granularity of data.

**Methods:** Using the PEDSnet research network of >11 million records, we refined a published computational phenotype (Denburg et al 2019) for a pediatric nephrotic syndrome (rFSGS) After Kidney Transplant (KTx) Through Comparable Phenotypic Algorithm Analyses of Multicenter Data. We identified children <19 years of age who underwent kidney transplantation in a single center were evaluated: 49 (13.1%) received a single graft from a small pediatric donor (≤15Kg, SPD group), 244 (65.1%) from a bigger pediatric donor (>15Kg, BPD group) and 82 (21.9%) from adult living donors (group ALD). After 5 years, the eGFR of ALD group was 10 ml/min/1.73m² inferior to the others. At that time, the eGFR from SPD group was statistically similar to the BPD (p=0.952).

**Conclusions:** In a specialized transplant center, the use of small single pediatric donor kidneys is as successful as bigger pediatric donors or adult living donors in transplants after 5 years of follow-up.

PO1972

**Prevalence and Progression of Pediatric CKD in a Large National Cohort**

Zahin J. Modi, Jonathan P. Troost, Kevin J. Dombkowski, Debbie S. Gipson. University of Michigan, Ann Arbor, MI.

**Background:** National prevalence and disease progression for pre-ESKD chronic kidney disease in children (pCKD) are not well described.

**Methods:** Data for children <19 years of age were extracted from the IBM MarketScan commercial and Medicaid databases for the years 2009-2018. pCKD prevalence estimates were calculated using stage-specific ICD-CM diagnosis codes (S85 and N18) and additional established qualifying pCKD codes. Survival curves were created to estimate the probability of reaching ESKD, stratified by type of CKD code utilized (stage-specific vs other codes).

**Results:** We identified children <19 years with commercial insurance (n=42,051,432) and Medicaid (n=13,610,450) over the 10-year period. Among these children, we found 197,318 with pCKD among those with commercial insurance (47 per 10,000) and 101,361 among those with Medicaid (74 per 10,000). pCKD stage-specific diagnoses were infrequently reported (commercial insurance:12%; Medicaid: 14%). Among the children with pCKD, 30% with commercial and 35% with Medicaid had multiple years of follow-up. Survival curves over the 10-year study period showed the majority of the progression to ESKD was among those with stage-specific pCKD (Figure).

**Conclusions:** In a large national cohort, 298,679 children with pCKD were identified over 10 years, with higher period prevalence in Medicaid-insured children. Stage-specific information was available for a small proportion of children, but when present was associated with a higher probability of reaching ESKD. This data suggests that children with conventional, staged CKD codes are more likely to have rapid progression while other codes that qualify for pCKD may capture children with kidney disease that are slower to progress.

**Funding:** Other NIH Support - NCATS, Private Foundation Support
Narrow Range of Plant-Protein Intake in the CKiD Cohort Does Not Demonstrate Changes in Estimated GFR

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Background: Vegetable or plant-based sources of protein may confer health benefits in children with progressive kidney disease. There is currently a knowledge gap in understanding the effect of different proportions of vegetable-based proteins on CKD progression in children.

Methods: The CKiD study is a multicenter, observational cohort of children with CKD. The Child Harvard Service Food Frequency Questionnaire (HSFFQ) was used to assess dietary intake. The proportion of vegetable protein (VP%) was defined as the fraction of plant protein to total protein intake. Statistical analysis used a mixed model with random intercept and slope to determine the effect on log-transformed changes in eGFR.

Results: This dataset included 2000 records on 631 subjects with a baseline eGFR from 30 to 90 mL/min/1.73m² calculated using CKiD Creatinine–Cystatin C 2012 formula. Across all dichotomized groups of children (sex, African American race, Hispanic ethnicity, etiology of CKD, hypertension, anemia, hyperkalemia, hyperphosphatemia, acidosis, BMI < 95th percentile) the median VP% was 32–35% regardless of group. Longitudinal mixed model analysis did not show any effect on eGFR due to changes in VP%.

Conclusions: Children with chronic kidney disease obtain about a third of their protein intake from plant or vegetable-based sources. More than 90% children in the CKiD cohort had a VP% that was less than 50% of total protein intake. Due to the narrow homogeneity of dietary patterns, there was no effect on the change in eGFR with changes in VP%.

Funding: NIDDK Support, Private Foundation Support
The Optimal Equation of Estimated Glomerular Filtration Rates for Pediatric CKD Patients in Transition from Adolescent to Adult: Results from KNOW-PedCKD
Seon Hee Lim,1 Eujin Park,1 Kyoung Hee Han,4 Seong heon Kim,1 Heeyeon Hee,5 Seong-Su Koh,3 Jae Il Shin,3 Min Hyun Cho,10 Joo Hoon Lee,7 II-Soo Ha,1,2 Hee Gyung Kang,2,3 Peong Gang Park,4 Yo Han Ahn,2,3 1Uijeongbu Eulji Medical Center, Uijeongbu-si, Gyonggi-do, Republic of Korea; 2Seoul National University College of Medicine Department of Pediatrics, Jongno-gu, Seoul, Republic of Korea; 3Seoul National University Children's Hospital, Seoul, Republic of Korea; 4Seoul National University College of Medicine, Seoul, Republic of Korea; 5Jeju University Hospital, Jeju, Republic of Korea; 6Pusan National University Hospital, Busan, Republic of Korea; 7Ministry of Health and Welfare, Sejong, Republic of Korea; 8Hallym University Medical Center, Yeongdeungpo-gu, Seoul, Republic of Korea; 9Samsung Medical Center, Gangnam-gu, Seoul, Republic of Korea; 10Severgence Hospital, Seodaemun-gu, Seoul, Republic of Korea; 11Kyungpook National University School of Medicine, Daegu, Daegu, Republic of Korea; 12Asan Medical Center, Songpa-gu, Seoul, Republic of Korea.

Background: Estimated glomerular filtration rate (eGFR) is an important value in kidney function evaluation, and it is useful to identify chronic kidney disease (CKD) and its progression. Clinicians use various equations to calculate eGFR which is based on serum creatinine (Cr) or cystatin C (CysC) concentration with other variables such as age, sex, and height. However, there is a lack of consensus on which equation is proper for patients in transition from adolescent to adult. Therefore, we evaluated the reliability of various eGFR calculation methods compared to measured isotope GFR (iGFR) in adolescents and young adults with CKD.

Methods: Seventy-three patients aged from 15 to 23 years were included in the KNOW-PedCKD cohort study for Outcome in patients With Pediatric Chronic Kidney Disease. We compared measured iGFRs with various eGFR calculation equations; the bedside serum Cr based equation (Schwartz), the CysC based equation (Schwartz), combined Cr and CysC-based Chronic Kidney Disease in Children equation (CKD-EPI Cr/CysC), the Chronic Kidney Disease in Children equation (CKD-EPI Cr/CysC), combined Cr and CysC-based Chronic Kidney Disease in Children equation (CKD-EPI Cr/CysC), and combined Cr and CysC-based Chronic Kidney Disease in Children equation (CKD-EPI Cr/CysC).

Results: Fifty-two (71.2%) patients were male and 86.3% of patients had non-glomerular causes of CKD. A total of 136 measurements of iGFR was performed at the median age of 17.0 (interquartile range (IQR) 16.0–18.8) years. The mean iGFR was 42.2 ± 29.0 mL/min/1.73m². The Schwartz equation had lowest bias (0.6 mL/min/1.73m²), high correlation (0.96), and highest accuracy (81.6% within 30% of iGFR). In the descriptive analysis, box plots displayed that anemic patients had a tendency towards lower scores than non-anemic patients. In the IPW-weighted analysis, subjects who were anemic were found to have worse Picture Vocabulary Test (U=23), Crystallized Cognition (U=22) and Total Cognition (U=19), but better Pattern Comparison (U=35), Working Memory (U=32) and Fluid Cognition (U=22). However, using the test-only, only Picture Vocabulary Test (p=0.02) and Crystallized Cognition Composite (p=0.03) were significantly different between the groups, with the anemic group performing more poorly than the non-anemic group.

Conclusions: Children with CKD and anemia had significantly lower scores on Picture Vocabulary and on the Crystallized Cognition Composite compared to non-anemic patients after adjusting for covariates, with moderate to large effect sizes. These results suggest that anemia may be a modifiable determinant of cognitive outcomes in children with CKD.

Funding: NIDDK Support

The Effect of Anemia on Neurocognition in Children with CKD
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Background: Chronic kidney disease (CKD) has been shown to affect neurocognitive outcomes. Anemia is associated with CKD and has been associated with a decrease in neurocognition in adults with CKD. Few studies have looked at neurocognitive outcomes in children with both CKD and anemia. This study’s purpose is to evaluate the impact of anemia on neurocognition in children with mild to moderate CKD.

Methods: Participants were >7 y and in the Chronic Kidney Disease in Children Study (CKiD) with NIH Cognitive Toolbox data. Anemia was defined as hemoglobin < 5th percentile for age, sex and race or use of an Erythropoietin-Stimulating Agent. All outcomes were compared between anemic and non-anemic groups descriptively using box plots, t-tests, and the magnitude of differences using Cohen's d statistic for effect size. Inverse probability weighting (IPW) was used to align the non-anemic and anemic groups on sex, estimated GFR level, urine protein/creatinine ratio, disease etiology, kidney history, hypertension and maternal education.

Results: 87 subjects total (25% with anemia) met criteria. Prior to weighting, groups were similar in age (17.9 vs 17.1 y, anemic vs non-anemic) with the anemic group trending towards a higher male percentage (73 vs 52%), and lower baseline eGFR (42 vs 64 mL/min/1.73m²). In the descriptive analysis, box plots displayed that anemic patients had a tendency towards lower scores than non-anemic patients. In the IPW-weighted analysis, subjects who were anemic were found to have worse Picture Vocabulary Test (U=23), Crystallized Cognition (U=22) and Total Cognition (U=19), but better Pattern Comparison (U=35), Working Memory (U=32) and Fluid Cognition (U=22). However, using the test-only, only Picture Vocabulary Test (p=0.02) and Crystallized Cognition Composite (p=0.03) were significantly different between the groups, with the anemic group performing more poorly than the non-anemic group.

Conclusions: Children with CKD and anemia may significantly lower scores on Picture Vocabulary and on the Crystallized Cognition Composite compared to non-anemic patients adjusting for covariates, with moderate to large effect sizes. These results suggest that anemia may be a modifiable determinant of cognitive outcomes in children with CKD.

Funding: NIDDK Support

Adverse Events Following Rituximab Infusion in Children with Nephrotic Syndrome: A Systematic Review
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PO1978
Efficiency and Safety of Long-Term Use of Rituximab in Pediatric Patients with Nephrotic Syndrome
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Background: Rituximab (RTX) is an effective therapeutic agent widely used in children with nephrotic syndrome (NS). However, long-term effects after the B cell depleting treatment remain unclear. We investigated the efficiency and safety of long-term use of RTX in pediatric NS patients.

Methods: We retrospectively reviewed the medical records of 58 patients with steroid-dependent or steroid-resistant NS who had received more than 3 cycles of RTX. Each cycle consisted of one to four infusions of RTX (375 mg/m² per dose) until the depletion of B lymphocytes.

Results: The first cycle of RTX was started at the median age of 12.1 (interquartile ranges [IQR] 8.8–14.1) years. Median 5 (IQR 4–8) times of RTX cycles were used during a period of median 4.0 (IQR 2.3–5.9) years. The B lymphocytes recovered to 1% at a median 5.7 (IQR 4.8–6.7) months after the completion of RTX administration. The relapse significantly decreased from median 2.0 (IQR 1.0–3.0) times per year to 0.2 (IQR 0.1–0.5) times per year after long-term RTX treatments (<0.001). Height growth and hypertension improved significantly compared with prior to the long-term use of RTX. (P<0.05).

Conclusions: The majority of children receiving RTX for NS do not experience serious AE/SE and RTX is generally well-tolerated. However, standardized reporting of AE/SE including timing, duration, and severity grade is warranted in future studies.

Conclusions: Long-term therapeutic use of RTX could be effective and relatively safe in pediatric patients with NS. However, impaired immunity should be monitored and carefully followed up during the long-term use of RTX.

PO1979
Rates of Idiopathic Childhood Nephrotic Syndrome Relapse During the COVID-19 Pandemic
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Background: While most children with idiopathic nephrotic syndrome (NS) enter remission after a course of steroid therapy, as many as 60–90% eventually relapse with recurrence of nephrotic-range proteinuria. Infections are thought to be primarily responsible for triggering relapses. The COVID-19 pandemic promoted physical distancing, face mask, and greater attention to infection prevention measures resulting in decreased transmission of common viral infections. We hypothesize that there will be a decreased rate of NS relapse during this period.

Methods: We conducted a retrospective chart review of children with NS followed at our center. Patients were identified by ICD 9/10 code for proteinuria and included if they had primary steroid-sensitive NS. Numbers of relapses and hospitalizations each year were collected for baseline data, March 1, 2015-March 1, 2020, and for the social distancing period (SDP), March 1, 2020-March 1, 2021.

Results: 117 children with NS were identified. The rate of relapse per year and the rate of hospitalizations per year were lower during the SDP compared with baseline pre-pandemic levels (76 vs 81 relapses per year and 14 vs 19 hospitalizations per year, respectively). Importantly, within a year of NS diagnosis, there was a baseline pre-pandemic increase of 1.6 relapses per patient. This was much lower for patients in the SDP with an average of 0.6 relapses per patient during the SDP (p<0.001). In contrast, there was no difference in new diagnoses of NS comparing SDP vs baseline period (15 vs 14 new cases per year).

Conclusions: Our results support our hypothesis of lower rates of NS relapse and hospitalizations during SDP. Most notably, there were significantly fewer relapses within the year following NS diagnosis during SDP compared with baseline. This is likely attributable to decreased transmission of common infections and greater attention to infection prevention by caregivers. Less hospitalizations during the SDP would suggest decreased severity of relapse, perhaps due to earlier detection, increased caregiver awareness, or fewer infections. Interestingly, the number of new diagnoses was similar. Future analysis will focus on identification of relapse triggers and associations with steroid responsiveness and other demographic characteristics.

PO1980
Sparosentan for Treatment of Pediatric Patients with Selected Proteinuric Glomerular Diseases: Design of the Phase 2 EPPIK Study
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Background: Sparosentan is a novel Dual Endothelin Angiotsensin Receptor Antagonist (DEARA) being investigated for focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN). It is a dual acting, highly selective antagonist of both the endothelin A receptor (ETAR) and the angiotensin II subtype 1 receptor (AT1R). The Phase 2 EPPIK study will examine the long-term antiproteinuric and nephroprotective potential and safety of sparosentan in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS).

Methods: The global, open-label, single-arm, multicenter study will evaluate the safety, efficacy, and pharmacokinetics (PK) of sparosentan in 57 patients (aged ≥1 to <18 years), including ~30 with FSGS and/or MCD (population 1) and ~27 with IgAN, IgAV, or AS (population 2) over 108 weeks (Figure). See Table for inclusion/exclusion criteria. Sparosentan will be administered in a novel liquid formulation at a dose adjusted to body weight.

Results: Primary endpoints include safety (incidence of treatment-emergent adverse events) and change in urine protein/creatinine ratio (UP/C) from baseline over 108 weeks of sparosentan treatment. Secondary endpoints include PK outcomes, change from baseline over 108 weeks in albumin/creatinine ratio and eGFR, and the proportion of patients with FSGS/MCD who achieve partial remission (UP/C ≤0.5 g/m² and ≥40% reduction in UP/C).

Conclusions: This Phase 2 study will evaluate the long-term safety, antiproteinuric, and nephroprotective effects of sparosentan in pediatric patients.

Funding: Commercial Support - Traverse Therapeutics Inc, San Diego, CA.

Table. Key Inclusion and Exclusion Criteria

Figure. Study Design
Efficacy of New Combination Therapy with Prednisolone, Mizoribine, and Lisinopril for Severe Childhood IgA Nephropathy

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Background: Our previous RCT shows that warfarin and diprifiramide added to prednisolone (PSL) and mizoribine (MBZ) in the 2-year combination therapy have additional effect for proteinuria remission in severe (diffuse mesangial proliferation, WHO) childhood IgAN compared to that with only PSL and MBZ (Pediatr Nephrol 2018;33:2103-12). However, we have to consider avoiding the use of warfarin and diprifiramide due to side effects. Meanwhile, angiotensin-converting enzyme inhibitors such as lisinopril have been widely used for childhood IgAN since the 2000s. Therefore, we intended to examine the effect of new combination therapy including PSL, MBZ, and lisinopril.

Methods: This cohort study included 84 patients with severe IgAN enrolled among 546 pediatric IgAN between 1977 and 2017, and divided into 2 groups, 70 patients treated with the previous combination therapy and 14 patients with the new combination therapy. A 1:1 propensity score matching was performed to account for between-group differences and 12 matched pairs were obtained.

Results: Proteinuria remission was significantly more obtained in the new treatment group (100% vs 30.0%, p=0.001). The patients with the new treatment achieved significantly faster proteinuria remission (median 2.4 vs. 12.0 months, p=0.04). The median duration of PSL use was significantly shorter in the new treatment group (13 vs. 24 months, p=0.0001). The median observation period was 4.9 and 4.5 years, and the percentage of patients with normal urine at the latest observation was significantly higher in the new group (66.7% vs. 25.0%, p=0.04).

Conclusion: Our findings suggest the usefulness of the new combination therapy with PSL, MBZ, and lisinopril for severe childhood IgAN in achieving early proteinuria remission and shortening PSL use. Further investigations with the larger-scale and long-term outcome will be needed.

PO1982
Renal Activity Index in Lupus (RAIL) Score Distinguishes Responder and Non-Responder in Pediatric Lupus Nephritis

Ellen Cody, Scott E. Wenderfer, Qing Ma, Angela Merritt, Prasad Devarajan, Hermine Brummer.

Systemic Lupus Erythematosus (SLE) is a diagnostic and therapeutic challenge, particularly lupus nephritis (LN). We described a composite score, the Renal Activity Index for Lupus (RAIL), consisting of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemotactic protein 1 (MCP-1), adiponectin, hemopexin and ceruloplasmin, where higher scores reflect more active inflammation on biopsy. We hypothesize that when followed longitudinally during induction therapy, a change in RAIL score distinguishes clinical responders from non-responders.

Methods: Pediatric patients (<18 years) diagnosed with LN were included (IRB #2008-0635). Diagnosis was made according to ACR criteria for SLE with renal biopsy in early disease detection and intervention.

Results: A change in RAIL during induction therapy is promising for predicting responders vs non-responders, with average decrease of 1 compared to no change. To further evaluate, more samples are needed, which is on-going.

Funding: NIDDK Support, Private Foundation Support

PO1983
Collapsing FSGS in Siblings with Compound Heterozygous Variants in NUP93 Expand the Spectrum of Kidney Phenotype Associated with NUP93 Mutation

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Introduction: Focal segmental glomerulosclerosis (FSGS) is a major cause of end stage kidney disease, the collapsing form has the worst prognosis. Study of families with hereditary FSGS has provided insight into disease mechanisms. In this report, we describe a sibling pair with NUP93 mutations and collapsing FSGS. This is the first report of collapsing FSGS associated with NUP93 mutations.

Case Description: We identified a Caucasian sibling pair with early onset steroid resistant nephrotic syndrome. Kidney biopsy in both brothers performed at ages 5 and 2 years, respectively, showed collapsing FSGS. Lesions of segmental or global sclerosis with focal collapsing features involved 22/33 and 6/28 glomeruli, respectively. Clinical phenotypes are summarized in Table 1. We obtained DNA from the affected brothers and their unaffected parents and carried out whole genome sequencing on the two affected siblings. We applied our standard filtering algorithm and identified segregating rare compound heterozygous variants 1) C.1772G>T p.G591V, 2) c.2084T>C p.L695S in NUP93 in the two affected brothers. Both variants are rare with minor allele frequency <0.00015. Both variants are evolutionarily conserved and were predicted to be pathogenic by four in-silico tools. 3D modeling revealed that both variants created structural alterations throughout the protein including the amino and the carboxyl terminal residues. These structural alterations are predicted to alter the binding affinity for several NUP93 ligands, likely disrupting the function of the highly organized nuclear pore channel.

Discussion: To the best of our knowledge, this is the first report of collapsing FSGS in patients with NUP93 mutations. Functional studies to determine the mechanisms by which these variants cause podocytopathy may provide insight into the pathogenesis of the more common idiopathic and virus-mediated forms of collapsing FSGS as well as aid in early disease detection and intervention.

Table 1 - Clinical Phenotypes

PO1984
Leukocyte-Derived Human RNase 6 and RNase 3 Provide Resistance to Urinary Tract Infection

Juan de Dios Ruiz-Rosado, Hanna H. Cortado, Macie M. Kercsmar, Ashley Jackson, Baring Li, Brian Becknell.

Background: Urinary tract infections (UTIs) account for 7 million office visits and $1.6 billion dollars in health care spending annually in the United States. Uropathogenic Escherichia coli (UPEC) is the primary etiological pathogen causing over 80% of UTI. Currently, there is a critical need for innovative and effective strategies to treat UTI and prevent Uti-associated sequelae. Antimicrobial peptides (AMPs) are fundamental components of the innate immune system that serve instrumental roles in eliminating pathogenic microbes and thus represent a potential therapeutic tool to limit UTIs. We have identified AMPs within the Ribonuclease (RNase) A Superfamily that promote resistance among uropathogens. In this study, we determined the contribution of human RNase 6 and 3 to bacterial clearance following experimental UTI in vivo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

610
Methods: Humanized RNASE6 and RNASE3 transgenic mice (C57BL/6) were generated by stereotaxic transgenesis. RNASE6 or RNASE3 genome fragments were inserted into the mouse genome. Humanized RNASE6-expressing or RNASE3-expressing female mice were transurethrally infected with UPEC strain UTI89. Transgenic littersmates were used as negative controls. Bone marrow-derived macrophages (BMDMs) and BM neutrophils (PMNs) from RNASE6 and RNASE3 transgenic mice were collected and infected with UPEC in vitro. RNASE6 and RNASE3 expression were determined by western blot, flow cytometry and immunofluorescence. Bacterial burden was assessed via quantification of UPEC colony forming units.

Results: RNASE6 transgenic mice showed reduced bacterial burden in the urine and bladder compared to non-transgenic mice following UPEC infection. F480 macrophages in the infected bladder were identified as the main source of RNASE6, while RNASE3 was predominantly expressed by Ly6G+ neutrophils in the bladder submucosa. We found that BMDMs from RNASE6 transgenic mice had reduced intracellular bacteria compared to WT BMDMs after UPEC infection in vitro. Decreased extracellular bacterial burden was observed in cell cultures from RNASE3 transgenic PMNs compared to non-transgenic PMNs.

Conclusions: Our findings indicate that RNASE6 and RNASE3 produced by innate phagocytes have a critical anti-microbial role against UPEC in vivo and in vitro. These RNases have the potential to effectively limit or prevent UTIs.

Funding: NIDDK Support

Human Bladder Tissues Express Gb3 and Are Targeted by Shiga Toxin

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Background: Shiga-toxin (Stx) producing E. coli (E. coli) will guide the selection of proper animal models for investigating the impact of Stx on urinary tissues. Finally, our study revealed that Gb3 mediate bladder inflammatory cell infiltration and transitional cell necrosis in Stx treated C57 WT mice.

Funding: Other NIH Support - Borroughs Wellcome Fund

Methods: We first established and validated two complementary detection methods for Gb3 on cultured cells, one with a monoclonal Gb3 antibody and the other detecting Gb3 with a monoclonal antibody against Stx.

Results: Gb3 is detected on the cell surface of WT 5637 cells, but not on A4GALT K0 cells. We found that normal human bladder connective tissue and vascular endothelial cells express Gb3, which mediates binding of Stx. Gb3 expression was detected in Yorkshire pig, New Zealand white rabbit, CD1 and C57 mouse, but not in Dolly sheep. Exposure to Stx induced a large amount of the Gb3 synthesized in the bladder submucosa in C57 mice, and bladder transitional cell necrosis was detected by pathological evaluation, while the transitional cells of A4GALT K0 mice showed no corresponding changes.

Conclusions: Here we report the novel finding that Gb3 is expressed within bladder tissues and may suggest that bladder tissues could be a key target of Stx in mice. Furthermore, we found that Gb3 expression varies among different animal models, which will guide the selection of proper animal models for investigating the impact of Stx on urinary tissues. Finally, our study revealed that Gb3 mediate bladder inflammatory cell infiltration and transitional cell necrosis in Stx treated C57 WT mice.

Funding: Other NIH Support - Borroughs Wellcome Fund

Renal-Derived Alpha-Defensins 1-3 Contribute to Enhanced Urinary Tract Protection in Humanized Mouse Transplant Model Challenged against Uropathogenic Escherichia coli

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Background: Alpha-defensins 1-3 are potent antimicrobial peptides expressed from DEFA1A3 gene locus by human neutrophils and kidneys. Decreased DNA copy numbers of DEFA1A3 have been associated with UTI susceptibility. Here, we utilize a humanized murine system to knock-in transgenic mouse (Defa1A3 KO) to study the role of Defa1A3 in UTIs. We hypothesized that Defa1A3 protects the murine urinary tract from uropathogenic E. coli (UPEC) challenge and renally derived Defa1A3 is the protective source.

Methods: Female wild-type (WT) and Defa1A3 mice were infected by transurethral inoculation of UPEC, CFT073, pyelonephritis strain. Bacterial burdens in kidneys and bladders for each group of mice were analyzed at 6 hours post-infection (hpi).

Results: We performed transplant isografts of Defa1A3+ KO mice and used WT + KO as biological controls for UPEC challenges (Figure 1A). Results: Murine bladder and kidney CFU bacterial burdens results are presented in Figure 1: Comparing the groups at 6 hpi, CFU burden averages were significantly lower in the Defa1A3→ WT recipient infected bladder, similarly to infected Defa1A3 mice when compared to its WT counterpart (B). Strikingly, kidneys from Defa1A3→ WT recipient were protected against bacterial growth, in contrast to WT→ KO→ WT recipient controls, which showed higher titers of CFU burdens per transplanted kidney following pyelonephritis challenge, and recapitulates the protective phenotype observed in the Defa1A3 infected mice when compared to its WT control group (C).

Conclusions: Our findings support the role of renal-derived alpha-defensins 1-3 in not only protecting the transplanted kidney but the entire lower urinary tract from UPEC.

Funding: NIDDK Support

Intercalated Cells Activate Innate Immune Defenses in Response to Uropathogenic Escherichia coli

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Background: Urinary tract infections (UTI), including pyelonephritis, are common in children. Intercalated cells (IC), positioned in the renal collecting duct, prevent and combat UTI by secreting antimicrobial peptides (AMPs) into the urine. The mechanisms regulating IC AMP production during UTI are unclear. Here, we challenged ICs in vitro with uropathogenic E. coli (UPEC) or bacterial cell membrane components to define the innate immune responses that control AMP production during UTI.

Methods: ICs (Clone C) were infected with a UPEC pyelonephritis strain (CFT073) or challenged with UPEC cell membrane components including lipopolysaccharide (LPS), muramyl dipeptide (MDP) and β-1,4-Glu-mDAP (E-DAP). Following stimulation, IC lysates were collected, and 87 immune genes were profiled using an antimicrobial response PCR array or targeted qRT-PCR. Western blot was performed to identify which innate immune responses are activated.

Results: In response to UPEC, ICs temporally activate immunomodulatory pathways and AMPs. Analysis of the PCR array data via STRING and Ingenuity Pathway Analysis identified 15 upregulated genes associated with Toll-like receptor (TLR), NOD-like receptor (NLR), and NF-kB signaling 4 hours post infection. Immunoblotting confirmed downstream targets in these pathways are activated in response to UPEC. qRT-PCR identified that AMPs like Lcn2 are activated while others, including RNASE6, are suppressed. Upon stimulation with LPS, qRT-PCR showed upregulation of Lcn2, Defa1, Defa3, and RNASE6 – suggesting that TLR4 activation may regulate the expression of these AMPs. Additionally, qRT-PCR showed Lcn2 was induced in response to the NOD2 agonist, MDP, while AMP expression did not change with the NOD1 agonist, fMLP.

Conclusions: During UPEC infection, TLR, NLR, and NF-kB responses are activated in ICs. Activation of TLR and NLR signaling may induce downstream targets like AMPs. Confirmation studies are needed to determine how these pathways regulate AMP expression and their differential regulatory targets. Identification of these nodes may serve as future targets to increase AMP production as an additional means to treat UTIs in children and adults.

Funding: NIDDK Support

Fate-Mapping Supports a Linear Model of Urothelial Formation and Regeneration

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Background: Urothelium is a highly specialized, slow turnover epithelium that lines the kidney, ureter, bladder and proximal urethra. Bladder urothelium contains several cell types organized into basal (B), intermediate (I) and superficial (S) cell layers. The progenitor responsible for urothelial repair has been the focus of many investigations, with
strong support for both B and I cell contenders. We have previously demonstrated that keratin (K5) urothelial cells (UCs) are context specific progenitors in the kidney. Here, we mapped the fate of K5-UCs across development and following cyclophosphamide (CYC)-induced urothelial injury in the bladder.

**Methods:** Using tamoxifen (TMX)-inducible Krt5ERT2-Cre; Rosa26loxP mice, we performed lineage tracing with zsGreen (zsGreen5) across development and evaluated their capacity to form I and S cells during homeostasis or following CYC-induced urothelial injury. Immunofluorescence microscopy was used to determine whether zsGreen5-UCs were K5 (B-cells), Uroplakin (Upk) (I; and S-cells), or K20 (S-cells). Organoid formation was used to evaluate progenitor capacity in vitro.

**Results:** Baseline analysis of our Cre;LoxP strategy confirmed that zsGreen5 is specifically expressed in basal K5-UCs 24h after TMX administration at all induction stages. The fate of zsGreen5-UCs varied, with neonatal (postnatal day 1) P7, P17 stages giving rise to adult (P42) I and S cells, the juvenile (P14) stage giving rise to I but not S cells, and adult (P35, P42) stages not escaping the B cell cycle. CYC-induced urothelial injury did not engage adult zsGreen5-UCs for repair, whereas neonatal and juvenile zsGreen5-UCs gave rise to I and S cells following CYC treatment. Organoid forming assays confirmed that zsGreen5-UCs could form organoids that express B and I cell markers, and neonatal UCs formed larger organoids than adult UCs.

**Conclusions:** We show that precise temporal populations of K5-UCs form I cells during homeostasis which in turn are engaged as adults for S cell formation in response to injury. We believe that these findings unite B and I cell progenitor models, by temporally linking a linear progression of B→I→S cell formation. A more complete understanding of the role of discrete urothelial cell populations will enable precise control of urothelial cell differentiation and will inform targeted tissue regeneration strategies.

**Funding:** NIDDK Support

**PO1999**

Urothelial Injury Triggers Adaptive Remodeling That Limits Congenital and Acquired Obstructive Nephropathy

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**Background:** Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Both congenital and acquired obstruction induce renal urothelial cells to remodel and assume a bladder-like morphology, but the mechanisms and significance of these changes remain unclear. We hypothesize that urothelial remodeling occurs as a consequence of injury to Uropakin (UPK) expressing cells and serves to attenuate obstructive nephropathy.

**Methods:** Urothelial injury markers were measured by ELISA in children undergoing pyeloplasty for congenital ureteropelvic junction obstruction (UPJO) versus non-obstructed controls. Male and female mice underwent acquired UPJO via unilateral ureteral obstruction (UO). The fate of Upk+ cells during UO was traced through the use of Cre;LoxP mapping. The impact of Upk plaque loss on the kidney’s response to UUO was assessed through the use of Upk+ mice. The effects of Upk+ cell depletion during UO were gauged by administering diphertheria toxin (DT) to Upk+Cre; (Cre;LoxP) mice.

**Results:** Urine from children with congenital UPJO contains elevated urothelial injury markers — including KRT14, UPK2, and KRT20 — compared to unobstructed controls. Mouse with U0O exhibit urothelial apoptosis and increased mRNA and protein expression of urothelial injury markers. Lineage analysis of Upk+ cells demonstrates that UUO triggers a sequence of Upk protein downregulation, proliferation, and elaboration of a bladder-like urothelial plaque. When this process is disrupted via Upk depletion or depletion of Upk+ cells, UUO results in augmented tubular injury and interstitial fibrosis.

**Conclusions:** Urothelial injury is a conserved response to UTO and initiates a series of events that culminate in protective, bladder-like remodeling. The resulting expansion of Upk+ cells and production of urothelial plaque represent an essential adaptation to limit renal parenchymal injury during UTO.

**Funding:** NIDDK Support

**PO1990**

An Ethical Decision-Making Framework for Genomic Testing in Pediatric Kidney Disease

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**Background:** Technological advances and increased access have led to genomics expanding beyond the genetics specialty. As a result, non-genetic specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making around patient and test selection is required to ensure equitable access while expanding beyond the genetics specialty. As a result, non-genetic specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making around patient and test selection is required to ensure equitable access while expanding beyond the genetics specialty. As a result, non-genetic specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making around patient and test selection is required to ensure equitable access while expanding beyond the genetics specialty.

**Methods:** A three-stage approach was used: 1) review of the literature on decision-making for genomic testing in nephrology and other disciplines; 2) observation of approaches to genomic testing in the general nephrology clinic and the renal genetics clinic at an Australian pediatric hospital; 3) review and revision of the framework with key stakeholders, including clinical geneticists, genetic counselors, pediatric nephrologists, clinical ethicists, and families from the renal genetics service. The initial framework was modified until consensus from key stakeholders was reached.

**Results:** A decision-making framework was created. This framework outlines the key decision-making categories and sub-categories for patient selection, with corresponding questions to aid usage. A number of case studies were developed to demonstrate the framework’s application. Key factors influencing utilization of the framework were identified, particularly funding pathway, clinical environment, and patient population.

**Conclusions:** The framework will guide decisions around patient-selection for genomic testing, to maximize equity and utility.

**Funding:** Other NIH Support - T-32 Training Grant

**PO1991**

Genetic Testing and Biomarkers as Predictive Tools for Congenital Anomalies of Kidney and Urinary Tract (CAKUT)

Meredith Harris, Elif Erkan, Kenneth Kaufman. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**Background:** Cincinnati Children’s Hospital is 1 of ~5 centers offering fetal interventions (FI) (amnioinfusions/amnioshunts) & infant hemodialysis (HD) for oligo/ anhydramnios (OA), increasing survival from 17 to 50%. As a result of this unique survival of severe CAKUT population, more investigation into genetics & biomarkers in severe CAKUT needs to be performed, particularly in our growing bilateral multicystic dysplastic kidney (bMCDK) population (fatal at most centers). We hypothesize identification of novel genetic mutations & biomarkers will aid in determination of the clinical course of infants & mechanisms of nephropathy.

**Methods:** Inclusion criteria for severe CAKUT are women undergoing FI for OA or infants starting HD by 1 month of life. We obtained amniotic fluid (AF) during FI and blood from the mother, father, & infant for trios whole exome sequencing (WES). We performed ELISA testing on AF of 4 renal tubular biomarkers produced by fetal kidneys and validated in AF (NGAL, Cystatin c, Uromodulin and ET-1). Controls are 2nd trimester AF from infants without CAKUT.

**Results:** We enrolled 18 families with bMCDK & obtained 8 AF samples (2 MCDK). We performed WES on 5 trios (4 bMCDK) We identified 4 strong candidate genes (Table). Biomarker testing included 8 AF samples & 10 controls. All 4 biomarkers are significantly lower in severe CAKUT than controls & are lower in bMCDK than bladder obstruction, likely as the bMCDK population has less renal endowment. Biomarkers are lower in those with intrauterine demise compared to liveborn.

**Conclusions:** In patients with severe CAKUT, we detected strong candidate genes, implicated in embryo development. This population is enriched for genetic variants, likely due to severity of presentation. We validated 4 biomarkers in AF with correlations to diagnosis & survival. WES & biomarker testing are promising techniques to predict the course of severe CAKUT prenatally. Our goal is to develop a polygenic risk score to predict disease severity in utero based on genetic & biomarker data in this unique population.

**Funding:** Other NIH Support - T-32 Training Grant

**PO1992**

Genetic Kidney Disease: The Importance of Variants of Uncertain Significance

Ashley M. Gefen, Laura J. Castellanos, Pamela Singer, Abby M. Basalely, Christine B. Sethna. Cohen Children’s Medical Center, Queens, NY.

**Introduction:** Diagnosing genetic kidney disease has become more accessible with the advent of low-cost and rapid genetic testing. The Invitae nephrolithiasis (NL) panel is performed on 3 blood samples (mother, father, & infant). We identified 4 variants of uncertain significance (VUS) in 3 unrelated neonates (1 heterozygous for COL2A1, 1 compound heterozygous for FLH1, 1 for COL4A5). The corresponding NL reports were interpreted as negative.

**Case Description:** A 7-month-old, ex-full term, white female was referred to pediatric nephrology clinic for recurrent urinary tract infections (UTI). Review of systems was positive for nephrocalcinosis (NC). She had no allergies or family history. Physical exam was unremarkable. Kidney/bladder ultrasound showed bilateral medullary NC. Voiding cystourethrogram was normal. Laboratory evaluation showed hypokalemia.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
(129 mmol/L), anion-gap metabolic acidosis, hypercalcemia (13.9 mg/dL, ionized calcium 1.53 mmol/L), hypophosphatemia (2.8 mg/dL), hypophosphatemia (1.3 mmol/L), low serum albumin (14 13.9% familiar disease. Focal segmental glomerulosclerosis (FSGS) was diagnosed in 54/95 (56.8%), minimal change disease (MCD) in 20/95 (21.2%) and collapsing glomerulopathy in 12/95 (12.6%). 43/101 (42.6%) progressed to CKF in 29 months (12.0-61.9) and 9/29 (31%) had recurrence after kidney transplantation (KT). APOL1 high risk genotypes (HRG) were identified in 8/98 (8.2%) and were associated with later NS onset [11.0 (10.0-14.5) vs 2.7 (1.4-4.9) yr, p<0.001]. Mendelian causes were found in other 14/98 (14.3%) families: NPHS1=4, NPHS2=3, PLCE1=2, WT1=2, COQ2=1, and phenocopies in CUBN=1 and COL4A5=1, all APOL1 G0/G0. Poorer renal survival was observed in APOL1 HRG vs non-Mendelian/non-APOL1 HRG (p=0.001), and a trend in Mendelian vs non-Mendelian/non-APOL1 HRG (p=0.06). The APOL1 or Mendelian cases had no post-KT recurrence. Using Cox regression, age of onset <1yr (OR=6.5, CI:2.3-16.9, p<0.0007) or a 9yr (OR=3.3, CI:1.3-7.9, p=0.015) were associated with reduced renal survival, independently of genetic findings, as well as self-declared non-white (OR=2.6, CI:1.3- 5.64, p=0.01) and non-MCD histology (OR=14.2, CI:2.1-948, p=0.002).

Conclusions: Mendelian causes of SRNS/FSGS were identified in 14.3% - a lower rate than in PodoNET, SRSN Study Group and RaDar - and APOL1 HRG in 8.2% of patients in this admixed population with a low frequency of parental consanguinity. Genetics factors, age of NS onset, ethnicity and biopsy pattern were independently associated with progression to CKF.

PO1993
Genetic Causes for Congenital Nephrotic Syndrome: North American Mutations and the Contribution of Regulatory Factors
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Background: Congenital Nephrotic Syndrome (CNS) is a debilitating disease that affects children within the first few months of life and is characterized by severe proteinuria and loss of kidney function. A majority of CNS cases are caused by mutation of the NPHS1 gene, particularly in other countries. Our first aim was to determine the specific genetic causes for CNS in North America (NA). Our second aim was to determine the contribution of FOXC1, FOXL1, and GATA3 to NPHS1 transcription and nephron production, which could serve as potential drug targets for CNS therapy.

Methods: A retrospective chart review was performed to determine the prevalence of CNS mutations in NA. A survey was administered to members of the Pediatric Nephrology Research Consortium (PNRC) in CNS. A questionnaire was developed by a team of pediatric nephrologists and was administered to members of the Pediatric Nephrology Research Consortium (PNRC) via Qualtrics. In vitro studies to determine the impact of FOXC1, FOXL1, and GATA3 on NPHS1 transcription and nephron production were performed to determine the effect of these transcription factors on nephron production.

Results: We found the average age of CNS diagnosis was 2.6 months, with 60.3% of patients being female. Sixty-eight percent of patients underwent genetic testing for their CNS and a majority of patients (65.1%) had NPHS1 mutations, whereas 11.6% had NPHS2 mutations. Interestingly, 7.0% had both NPHS1 and NPHS2 mutations and 11.6% had only WT1 mutations. The remaining 4.6% had inconclusive results. We noted that the average age of onset for NPHS1-only mutations was 2.1 months, whereas patients with only NPHS1 mutations had an 6.3 years of age of onset of 4.5 months. Interestingly, patients with either WT1 mutations or a combination of NPHS1 and NPHS2 mutations had younger ages of onset of 1.35 months and 1.25 months, respectively. In our in vitro studies, siRNA knockdown of FOXC1, FOXL1, and GATA3 resulted in alterations in the expression of nephron.

Conclusions: The results of this study not only demonstrate the distribution of genetic causes for CNS in North America, but also show that transcription factors may play a role in NPHS1 transcription.

PO1994
Mendelian Causes Are Identified at a Relatively Low Rate and Show a Unique Pattern in Brazilian Pediatric Patients with Steroid-Resistant Nephrotic Syndrome or Focal Segmental Glomerulosclerosis
Andreas Wehmanen,1 Reciel D. Neves,1 Elieser H. Watanabe,1 Antonio M. Lerario,1 Denise M. Malheiro,1 Maria H Vaisbich,1 Friedhelm Hildebrandt,2 Matt G. Sampson,2 Luiz F. Onuchic,1 University of Sao Paulo, Sao Paulo, Brazil; Boston Children’s Hospital, Boston, MA; University of Michigan, Ann Arbor, MI.

Background: Genetic and non-genetic factors have been associated with faster progression to chronic kidney failure (CKF) in children with steroid-resistant nephrotic syndrome (SRNS). The contribution profile of such factors in admixed populations, however, is still not well characterized.

Methods: 101 patients/98 families with idiopathic SRNS, age of onset <18yr, were sequenced for 62 NS genes or submitted to whole exome sequencing. Causative variants and APOL1 risk alleles were confirmed by Sanger sequencing. Clinical data were retrospectively reviewed.

Results: Age of NS onset was 2.9yr (1.5-6.8), 61 (60.4%) were male, 61 (60.4%) self-declared white, 6 (5.9%) had parental consanguinity, and 14 (13.9%) familial disease. Focal segmental glomerulosclerosis (FSGS) was diagnosed in 307/95 (36.8%), minimal change disease (MCD) in 20/95 (21.2%) and collapsing glomerulopathy in 12/95 (12.6%). 43/101 (42.6%) progressed to CKF in 29 months (12.0-61.9) and 9/29 (31%) had recurrence after kidney transplantation (KT). APOL1 high risk genotypes (HRG) were identified in 8/98 (8.2%) and were associated with later NS onset [11.0 (10.0-14.5) vs 2.7 (1.4-4.9) yr, p<0.001]. Mendelian causes were found in other 14/98 (14.3%) families: NPHS1=4, NPHS2=3, PLCE1=2, WT1=2, COQ2=1, and phenocopies in CUBN=1 and COL4A5=1, all APOL1 G0/G0. Poorer renal survival was observed in APOL1 HRG vs non-Mendelian/non-APOL1 HRG (p<0.001), and a trend in Mendelian vs non-Mendelian/non-APOL1 HRG (p=0.06). The APOL1 or Mendelian cases had no post-KT recurrence. Using Cox regression, age of onset <1yr (OR=6.5, CI:2.3-16.9, p<0.0007) or a 9yr (OR=3.3, CI:1.3-7.9, p=0.015) were associated with reduced renal survival, independently of genetic findings, as well as self-declared non-white (OR=2.6, CI:1.3- 5.64, p=0.01) and non-MCD histology (OR=14.2, CI:2.1-948, p=0.002).

Conclusions: Mendelian causes of SRNS/FSGS were identified in 14.3% - a lower rate than in PodoNET, SRSN Study Group and RaDar - and APOL1 HRG in 8.2% of patients in this admixed population with a low frequency of parental consanguinity. Genetics factors, age of NS onset, ethnicity and biopsy pattern were independently associated with progression to CKF.

PO1995
Genetic Testing in Children with Nephrolithiasis and Nephrocalcinosis
Ashley M. Gofen,1 Christine B. Sethna,1 Onur Cil,2 Farzana Perwad,2 Meg Schoettler,2 Louise Amlie-Wolf,2 Jonathan S. Ellison,2 Daniel Feig,2 Joshua Zaritsky,3 'Cohen Children’s Medical Center, Queens, NY; ’Saint Christopher’s Hospital for Children, Philadelphia, PA; ’Alfred I DuPont Hospital for Children, Wilmington, DE; 4UCSF Benioff Children’s Hospital, San Francisco, CA; ’University of California San Francisco School of Medicine, San Francisco, CA; ’Medical College of Wisconsin, Milwaukee, WI; ’The University of Alabama at Birmingham School of Medicine, Birmingham, AL.

Background: Diagnosing genetic kidney disease has become more accessible with the advent of low-cost and rapid genetic testing. The study objective was to determine the sensitivity of genetic testing in diagnosing kidney disease in children with nephrolithiasis (NL) and nephrocalcinosis (NC).

Methods: A retrospective multicenter study was conducted on children ≥12 years with NL/NC that underwent the Invitae sponsored NL panel. Next-generation sequencing evaluated 55 genes. The sensitivity of genetic testing was calculated. Logistic regression examined the association of genetic diagnosis.

Results: Seventy-eight children from 5 centers were included (56 had isolated NL [INL] and 22 had NC). Sensitivity of genetic testing was 31% (INL 27%, NC 41%). Of those with genetic diagnoses (Figure 1), 25% had pathogenic mutations alone, 13% carried pathogenic mutations for recessive conditions, 13% carried a pathogenic mutation and variant of uncertain significance (VUS) in the same gene and 50% had VUS alone. Mutations were found in 25 genes, most commonly HOGA and SLC3A1 in INL and SLC3A4 and COL1A1 in NC. Clinical features are shown in Figure 2. In multivariate analysis, subjects with hypercalcemia were less likely to have a genetic diagnosis (OR 0.35, 95% CI 0.13-0.95, p=0.04).

Conclusions: This study has demonstrated the utility of genetic testing, where explanatory genetic mutations were found in one-third of children with NL/NC. Genetic testing shows promise to improve clinical practice in this population.
Experience from a Single Centre Following a Large Cohort of Children with Cystinuria (1996-2019)
Sergio Camilo Lopez Garcia,1,2 Naima Smelders,1 Wesley N. Hayes,3 Alexander Cho,1 Tom A. Watson,1 Alex Barnacle,1 Marina J. Easty,1 Detlef Bockenhauer,1,2 1Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; 2University College London London, United Kingdom

Background: Cystinuria is a rare monogenic disorder accounting for 5-10% of all paediatric urolithiasis cases. This study reviews epidemiologic, clinical and management data of a large, single centre cohort of cystinuric children.

Methods: Respectively data collection from children with cystinuria between June 1996 to April 2019 in our centre.

Results: A total of 52 (54% female) patients were identified with a median (IQR: interquartile range) age at presentation of 6.2 (1.9-10.3) years. 24/52 (46%) had affected family members. Common presenting symptoms were abdominal pain 21/51(41%), urinary tract infection (39%), haematuria (18%); 14/51(28%) cases were diagnosed by family screening or incidentally. 9/52(17%) had cystinuria but did not form a stone. At presentation stone location was upper tract in 30/43(70%), bladder stones were found in 10/43(23%). Estimated GFR <90ml/min/1.73m2 in 14/52(27%) at diagnosis.

Hyperhydration fluid target was met by 63% and 76% were prescribed alkali, median (IQR) dose was 0.50(3.0-7.7) meq/kg/day and urine pH 7.0(7.0-8.0). 24/52(46%) patients had 26 treatment periods with cystine-binding thiol drugs (CBTD) for a median (IQR) dose was 0.5(0.3-0.7) mEq/kg/day and urine pH 7.0(7.0-8.0). 24/52(46%) patients had 26 treatment periods with cystine-binding thiol drugs (CBTD) for a median (IQR) duration of 34(18-65) months; 7/24(29%) patients on CBTD developed adverse effects leading to discontinuation in 14/52(27%). Median follow-up was 341 patients were identified. Median age at CED was 9.4 years (IQR 5.0, 13.0). Median follow-up was 2.9 years (IQR 1.1, 6.0). Median eGFR was 117.33 ml/min (IQR 95.75, 139.79). Most patients with renal transplant were transplanted prior to CED. Similarly, dialysis (n=14) was initiated in the majority before CED and at a younger age than those starting dialysis after CED. Prescription drug therapy before CED was high (29% patients with B6 use, Table). Nephrology was the specialty most commonly responsible for initial PH diagnosis (69% on CED).

Conclusions: In one of the largest cohorts of children in the US with PH, dialysis and renal transplant occurred before diagnosis, suggesting significant morbidity when diagnosis is delayed. Medications for the organs affected by PH were consistently prescribed before diagnosis, suggesting an opportunity for earlier PH identification to enable tailored therapy to potentially delay or prevent need for dialysis and transplant.

Funding: Commercial Support - Dicerna Pharmaceuticals

Temporal Relationship of Transplant, Dialysis, and Medications for Children with Primary Hyperoxaluria
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Background: Primary hyperoxaluria (PH), a rare inborn error of metabolism resulting in massive overproduction of oxalate, causes kidney stones and, for some, end-stage renal disease and systemic oxalosis. Our objective was to determine the timing of dialysis, renal transplant, and use of medications to treat PH manifestations in children relative to their diagnosis.

Methods: A retrospective cohort study was conducted in PEDSnet, a clinical research network of 7 US pediatric health systems. Data from PEDSnet were queried to identify patients <18 years old with a diagnostic code for or related to PH between 2009 – 2020. Outcomes queried were renal transplant, initiation of dialysis, first prescription for medications used to treat end-organ manifestations of PH, and specialty care visits. Outcomes were evaluated relative to cohort entrance date (CED), defined as date of first PH-related diagnostic code.

Results: 341 patients were identified. Median age at CED was 9.4 years (IQR 5.0, 13.0). Median follow-up was 2.9 years (IQR 1.1, 6.0). Median eGFR was 117.33 ml/min (IQR 95.75, 139.79). Most patients with renal transplant were transplanted prior to CED. Similarly, dialysis (n=14) was initiated in the majority before CED and at a younger age than those starting dialysis after CED. Prescription drug therapy before CED was high (29% patients with B6 use, Table). Nephrology was the specialty most commonly responsible for initial PH diagnosis (69% on CED).

Conclusions: In one of the largest cohorts of children in the US with PH, dialysis and renal transplant occurred before diagnosis, suggesting significant morbidity when diagnosis is delayed. Medications for the organs affected by PH were consistently prescribed before diagnosis, suggesting an opportunity for earlier PH identification to enable tailored therapy to potentially delay or prevent need for dialysis and transplant.
CKD 1-5; n=48 patients), hemodialysis (HD; n=31), transplantation (Tx; n=32) and related to vitamin B6 medication. **Results:** From normal kidney function to CKD3-4 Pox remained stable (median Pox 17 µmol/l), while Pglyc was more markedly elevated (median 90.12 µmol/l). Both were significantly higher in non-B6 versus B6 sensitive patients. Pox and Pglyc did not correlate with kidney function, except for Pox and CKD5. Highest Pox and Pglyc was found in HD (91 and 211 µmol/l, respectively), not related to B6. Uox and Uglyc remained stable at all CKD stages in B6 sensitive, but increased progressively in B6 insensitive patients. Pox and Uox slowly declined post combined and sequential liver-kidney, but also in isolated kidney Tx, which was performed in adult B6-sensitive patients. In the contrary, Pglyc remained elevated post Tx.

**Conclusions:** Our findings are in many ways contradictory to previously published observations. Pox or Uox did not correlate to GFR. Pox was surprisingly low until HD and remained elevated until CKD3-4 in non-B6 sensitive patients. PGlyc remained elevated even years after transplantation, but no data are available to compare. Glycolate is widely increased until CKD3-4 in non-B6 sensitive patients. PGlyc remained elevated post Tx.

**Funding:** Government Support - Non-U.S.

**PO2000**

**Compassionate Use Treatment with RNAi Medication (Nedosiran) in Two Patients with Primary Hyperoxaluria Type 1 and Maintenance Hemodialysis**

Bernd Hoppe, Gesa Schalk, Cristina Martin Higuera. 1German Hyperoxaluria Center, Bonn, Germany; 2Kindernierenzentrum, Bonn, Germany.

**Introduction:** The primary hyperoxalurias (PH) are three ultra-rare, autosomal recessive genetic disorders characterized by oxalate overproduction in the liver. Hyperoxaluria induces recurrent kidney stones, nephrocalcinosis, progressive renal impairment, and systemic oxalosis, especially in PH1. Nedosiran is an investigational RNA interference (RNAi) therapeutic administered monthly by subcutaneous injection. It reduces hepatic LDHA protein thereby inhibiting the final step responsible of oxalate production in all types of PH.

**Case Description:** We report on two PH1 patients, a 40 year old woman (a) on hemodialysis (HD) 6 x 3 hours weekly, and a 6.5 year old boy (b) receiving 5 x 5 hours HD, both homozygous for AGXT c.508G>A and treated with pyridoxine. In patient (a), global longitudinal strain (GLS), an index of left ventricular contractibility, was impaired (-13%; normal ≤-18%). Patient (b), has massive oxalate osteopathy, myocardial hypertrophy and cardiac insufficiency (GLS of −9.9%). They received Nedosiran as compassionate use medication for now 6 months. Monthly plasma oxalate (Pox in µmol/l, normal <7.4) was measured, Speckle Echo and/or 3 Tesla bone MRI (left knee) were repeated. Speckle echo improved significantly in both (a: GLS −23%; b: GLS -16.5%). Bone MRI ameliorated in patient (b) showing a nidus of normal trabecular structure.

**Discussion:** Clinics improved and Pox declined over the six months of treatment. Pox was influenced in (b) by severe oxalate osteopathy and therefore possibly dissolving oxalate and in (a) when dialysis regimen was reduced to 4 x 3 hours at month 6. We cautiously conclude, that Nedosiran treatment reduces plasma oxalate levels in a way, that liver transplantation may be avoidable in PH1 patients.

**PO2001**

**Functional Analysis of Novel CNNM2 Mutation in Autosomal Dominant Hypomagnesemia with Seizure**

Min-hua Tseng. Chang Gung Medical Foundation, Taoyuan, Taiwan.

**Background:** CNNM2 has been identified to be the responsible gene for patients with hypomagnesemia, seizure, intellectual disability (HSMR) syndrome. The functional impact of mutations in CNNM2 remains unknown.

**Methods:** We have identified 1-year-old infant with HSMR featuring severe hypomagnesemia with intravenous magnesium (Mg2+) wasting requiring higher dose of Mg2+ supplementation. Whole exome sequencing (WES) with direct Sanger sequence was performed to identify the responsible gene. The functional assay of this identified mutants was examined in vitro studies.

**Results:** With WES, we identified a de novo heterozygous mutation c.G1439T (R480L) in CBS domain of CNNM2 gene with intravenous magnesium (Mg2+) wasting requiring higher dose of Mg2+ supplementation. Patient (b) by severe oxalate osteopathy and therefore possibly dissolving oxalate and in (a) when dialysis regimen was reduced to 4 x 3 hours at month 6. We cautiously conclude, that Nedosiran treatment reduces plasma oxalate levels in a way, that liver transplantation may be avoidable in PH1 patients.
PO2003

Walking in Patients’ Shoes: Novel Approach to Increase Staff Empathy Through Adherence to Dietary Restrictions

Randa Razzouk, Mary Cazzell, Amanda Marroquin, Barrett Brown. Cook Children’s Medical Center, Fort Worth, TX.

**Background:** Dietary recommendations for children with end-stage renal disease (ESRD) on dialysis include restrictions in potassium, phosphorus, and sodium. Children must take phosphate binders with meals and snacks. Renal diet compliance can be challenged by adherence difficulties. Patient perceptions of health care professionals (HCPs) levels of empathy play an important role in improved patient satisfaction. Higher perceived empathy levels lead to improved patient compliance to treatment, diet, and overall positive health. The purpose of this study was to explore the impact of a novel intervention (adherence to a two-week renal diet) on empathy among HCPs directly caring for children with ESRD on dialysis.

**Methods:** A quasi-experimental comparative interventional study design was utilized with a convenience sample of 37 HCPs who directly cared for children with ESRD on dialysis Through self-assessment, 14 HCPs completed a renal diet education class (control group); 23 completed the class and two-week renal diet and “phosphate binders” intake with logs (experimental group). Pre- and post-intervention levels of empathy were measured using the Jefferson Scale of Empathy. Renal diet logs were reviewed to calculate percentages of renal diet compliance and “phosphate binder” use.

**Results:** Baseline empathy scores for each group were matched (p=0.825). Within the experimental group, post-intervention results showed statistically significant increases in empathy levels after adherence to a two-week renal diet (p=0.004). No significant differences in control group pre- and post-empathy levels were noted. Percentages of compliance to a two-week renal diet were 82% and to “phosphate binders” 83%.

**Conclusions:** Levels of empathy increased when HCPs followed a two-week renal diet, discovering similar patient adherence issues. HCPs reported less-than-perfect renal diet compliance and use of “phosphate binders.” This study can be implemented in various pediatric settings, such as specialty areas treating patients on therapeutic dietary restrictions (e.g. diabetes, celiac disease, epilepsy).

Results from experimental group:

- **Diet Compliance:** Percentage of compliance to a two-week renal diet was 82%.
- **Phosphate Binder Use:** Percentage of compliance to “phosphate binders” was 83%.

PO2004

Outcome of a 30-Month Screening, Education, and Treatment Program of Lower Urinary Tract Dysfunction (Dys)Function in Pediatric Kidney Recipients


**Background:** Graft survival of pediatric kidney recipients increased dramatically over the past decades. Lower urinary tract dysfunction (LUTD) is a common problem among children with chronic kidney disease (CKD) and ESRD, which can significantly affect their quality of life. The purpose of this study was to evaluate the outcomes of a screening, education, and treatment program for patients with LUTD.

**Methods:** A total of 56 recipients are screened thus far, aged 11.8±6.0 years. The program included a 30-month screening, education, and treatment plan. The data was collected retrospectively from patient records.

**Results:** Of the 56 recipients screened, 48% had LUTD at the time of screening. Of those, 71% of the patients (Table 1) had an abnormal bladder capacity and 59% had an abnormal maximal bladder capacity. The median time after transplant was 4.4 months. A significant proportion of patients (0.86 versus 0.74) had an abnormal bladder capacity.

**Conclusions:** The screening, education, and treatment program was effective in 48% of the children with LUTD, indicating a positive impact on the treatment and education of these patients.

**References:**

- Table 1: Results of the screening, education, and treatment program of LUTD in pediatric kidney recipients.

PO2005

Machine Learning Can Predict the Individual Risk of Acute Pyelonephritis in Children

Olivier Niel, Pierre François, Claire Sommelette, Michel Kohnen, Chantal Tsobo, Isabel De La Fuente, Armand Biver. Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg.

**Background:** Acute pyelonephritis (AP) is a common infection in children. Timely diagnosis of pediatric AP is necessary, since under-diagnosed AP increases the risk of sepsis, whereas over-treatment of AP is responsible for an increase in antibiotic resistance and health costs. However, confirmed AP diagnosis requires validated urine cultures, which can take up to 3 days. Here we propose to use machine learning algorithms to predict the risk of AP in febrile children, using simple parameters available within the first hours of medical care.

**Methods:** We performed a retrospective study of medical and laboratory files of 102 pediatric patients with a suspected diagnosis of AP, treated between 2014 and 2020 at the pediatric National Reference Hospital of Luxembourg. Based on the results of urine cultures, patients were allocated to the AP or non-AP group. All patients were then randomly split into training and testing batches, used by a Random Forest machine learning algorithm to predict the individual risk of AP, using clinical (age, sex), blood (CRP, white blood cell and neutrophil counts) and urine (red and white blood cell counts) parameters.

**Results:** Patients’ demographic and clinical characteristics were comparable between groups. In particular, sex ratios were not significantly different between AP and non-AP patients (0.66 versus 0.74). Random Forest algorithm mean performance metrics were: accuracy 90.48% [85-99%], sensitivity 91.67% [90-95%], specificity 88.89% [90-90%]. Given a prevalence of AP of 60%, positive predictive value was 92.52% [89-95%], negative predictive value 87.67% [82-89%]; mean AUC-ROC was 0.92. Predictions were performed with a neural network or a support vector machine algorithm on the same population obtained comparable performance metrics.

**Conclusions:** Timely diagnosis of pediatric AP is necessary to minimize infectious morbidity, antibiotic resistance and health costs; however, it requires validated urine cultures, which can take several days. Here we showed that machine learning algorithms can accurately predict the individual risk of AP in pediatric patients within the first hours of medical care, helping pediatricians in daily clinical decision making.

**References:**

- Table 1: Characteristics of the study population and performance metrics of the Random Forest algorithm

PO2006

Associations Between Clean Intermittent Catheterization, Quality of Life, and Emotional-Behavioral Functioning in Children with CKD

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**Background:** Need for clean intermittent catheterization (CIC) can affect quality of life (QOL) and emotional functioning in pediatric populations, with some evidence that urethral catheterization is associated with poorer emotional adaptation than use of Mitrofanoff. Little is known about the impact of CIC on QOL and emotional functioning for children with chronic kidney disease (CKD).

**Methods:** Data from the CKiD study were used to evaluate QOL, emotions/behavior, and CIC in children age 6+ years with mild to moderate CKD (non-glomerular disease). We hypothesized that CIC would be associated with poorer QOL and more internalizing and behavioral problems (using ratings from BASC2, PedQL), and that urethral CIC (versus Mitrofanoff) would predict worse outcomes. Linear mixed models adjusted for sociodemographic and disease-related covariates were used and included predictors for CIC use (vs non-users) as well as for urethral catheterization (vs Mitrofanoff).

**Results:** The sample included 1484 records (466 CIC non-users, median age 10 years, 66% male, median eGFR 52 ml/min/1.73m²; 115 CIC users, median age 12 years, 67% male, median eGFR 45, 43% urethral, 48% Mitrofanoff). Median BASC2 scores...
were in the average range for both CIC users and non-users. Median PedQoL scores were slightly lower than that of healthy populations for CIC non-users (parent-report 80 [IQR=66,89]; child-report 79 [IQR=70,88]) and even lower for CIC users (parent-report 73 [IQR=59,83]; child-report 76 [IQR=65,85]). CIC predicted higher scores on the BASC2 Internalizing Composite (β=3.33, CI=1.13, 5.54; p<0.003), and Behavioral Symptoms Index (β=2.13, CI=0.08, 4.18; p=0.04), and lower parent- and child-reported QOL (β=5.11, CI=−8.46, 1.75; p=0.05; β=3.75, CI=−6.98, 0.52; p=0.02). However, urethral CIC predicted lower scores compared to Mitrofanoff on the Internalizing Composite (β=−3.94, CI=−6.65, −1.22; p<0.005).

Conclusions: For children with mild to moderate CKD, CIC is associated with poorer QOL and more parent-reported emotional-behavioral symptoms. Urethral CIC (versus Mitrofanoff) is associated with fewer internalizing symptoms. Additional research is needed to determine if other characteristics associated with need for CIC influence emotions and QOL.

Funding: NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI)

**PO2007**

Pneumococcal Vaccination in High-Risk Pediatric Nephrology Patients

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Background: Children with nephrotic syndrome (NS), chronic kidney disease (CKD) and immunosuppression (IS) are at high risk of invasive pneumococcal infection but are often under-vaccinated with PCV13 and PPV23. We aimed to increase vaccination rates in high-risk pediatric nephrology (PN) patients from <10% to 75% by 2022.

Methods: Process measures of vaccine rates (percent of eligible patients monthly that received vaccines) were evaluated over 3 years. Initially, a designated nurse and fellow checked electronic medical records (EMR), Citywide Immunization Registry (CIR) and pediatrician records. PPV23 was administered in PN clinic. A driver diagram was created to determine sources of improvement and 3 PDSA cycles were completed.

Results: 374 patients (20% up-to-date [UTD], 5% missing PCV13, 32% missing PPV23, 34% missing both) were identified. Sources of failure to vaccinate with initial interventions were single stakeholder reliance, lack of follow-up and vaccine supply. Primary drivers were patient identification, vaccine administration and rate determination. All physicians and nurses were taught to identify patients, check vaccine history and use a vaccine algorithm. Study of our interventions revealed unanticipated obstacles with monetary cost, vaccine refusal and shared responsibility. To aid monetary issues, a new stakeholder (manager) was created. Vaccines were re-offered at subsequent visits if initially refused. Reminders were sent to physicians on the importance of patient identification in clinic. Vaccination increased to >75% and has been sustained for 4 months (Figure 1). Percent UTD increased to 39%.

Conclusions: Incorporating and educating multiple stakeholders and adequate vaccine access improved vaccination rates at our center. Our methods appear successful without excess time expenditure. Further study is underway to ensure sustainability without excess monetary cost.

**PO2009**

Pediatric Nephrologists’ Perspectives on Palliative Care: A National Survey Study

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Background: Integration of palliative care (PC) within nephrology practice offers the chance to lessen the burdens experienced by children with chronic kidney disease (CKD) and their families. Yet, little is known about pediatric nephrologists’ attitudes regarding engaging in and seeking PC services for children with CKD. We sought to ascertain pediatric nephrologists’ perspectives in routine integration of PC for children with CKD.

Methods: A cross-sectional web-based survey was administered to pediatric nephrologists associated with the American Society of Pediatric Nephrology listserv. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was adapted from a previously validated instrument and pretested by stakeholders; studied areas included institutional and personal experience with PC, training and education, and patient confidence. Data were summarized descriptively.

Results: There were 64 participants (17.7% response rate). Most participants were female (62.5%), Caucasian (64.1%), and practice in urban (76.4%), academic centers (89.1%) with access to subspecialty PC teams (93.8%). Perceived institutional barriers to subspecialty PC consultations were low, and prior consultations were found to be helpful. However, nephrologists expressed concern that consultation may imply to parents that the team is “giving up” on their child. Though 63.6% indicated that consultation should happen at diagnosis for life threatening conditions where cure is feasible but may fail, 59.6% of nephrologists reported that PC is rarely or never consulted for ESKD patients at their center. Confidence in engaging in challenging communication was high, yet only 26.4% and 30.2% of participants, respectively, were comfortable managing pain or psychological distress of children with CKD.

Conclusions: Pediatric nephrologists are receptive to PC consultations for children with CKD, but utilization is low. Parental perception of the implications of consultation are of concern. Among primary PC skills, challenging communication is seen as a strength of pediatric nephrologists, but confidence is low in managing some physical and psychological symptoms. Routine integration of PC will require efforts to assess patient and family impressions of PC and shift that of providers, as well as targeted education to increase skills.

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (T32DK07662-30, PJ Hingorani).

**PO2010**

Palliative Care Training in Pediatric Nephrology Fellowship: A Cross-Sectional Survey

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Background: The integration of primary palliative care (PC) in pediatric nephrology provides an opportunity to address the burdens faced by children with chronic kidney disease (CKD) and their families. Incorporation of PC education in training programs is recommended, but adult nephrology fellows report inadequate preparation to engage in primary PC. Similar experience of pediatric nephrology fellows is unknown. We sought to determine pediatric nephrology fellows' knowledge and confidence in providing primary PC and PC education received during training.

Results: For children with kidney disease had an increased likelihood of 6.46 (CI= 0.78-54.05) times that seen in control sample for development of acute psychosis in AYA. While unable to rule out the observed effect being due to random chance, acknowledgement of the attributions made by restricted data samples into two groups: ICD-coding defined kidney disease vs healthy peer control. Data analysis uncovered ten of 1192 (Prevalence= 0.84%; OR= 0.008) cases experienced acute psychosis throughout AYA. One of these ten cases occurred in CKD sample, representing a 4.76% prevalence (OR= 0.05). The remaining nine cases of AYA psychosis occurred in the control sample, representing a prevalence of 0.77% (OR= 0.008).

Conclusions: Preliminary data demonstrate, those with kidney disease had an increased likelihood of 6.46 (CI= 0.78-54.05) times that seen in control sample for development of acute psychosis in AYA. While unable to rule out the observed effect being due to random chance, acknowledgement of the attributions made by restricted data samples into two groups: ICD-coding defined kidney disease vs healthy peer control. Data analysis uncovered ten of 1192 (Prevalence= 0.84%; OR= 0.008) cases experienced acute psychosis throughout AYA. One of these ten cases occurred in CKD sample, representing a 4.76% prevalence (OR= 0.05). The remaining nine cases of AYA psychosis occurred in the control sample, representing a prevalence of 0.77% (OR= 0.008).

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (T32DK07662-30, PJ Hingorani).
PO2011

Correlation Between Kidney Sodium and Potassium Handling and the Renin-Angiotensin-Aldosterone System in Children with Hypertension

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Background: Urine sodium and potassium concentrations are used as surrogate markers for dietary sodium and potassium consumption in adults with hypertension, but their association with components of the renin-angiotensin-aldosterone system (RAAS) is incompletely characterized. Some individuals with hypertension may have an abnormal RAAS response to dietary sodium and potassium intake, though this is incompletely described. Our objective was to investigate if plasma renin activity and serum aldosterone are associated with urine sodium and potassium in youth with hypertensive disorders.

Methods: This pilot study was a cross-sectional analysis of baseline data from 44 youth being evaluated for hypertensive disorders. We recorded urine sodium and potassium normalized to urine creatinine, plasma renin activity, and serum aldosterone values and calculated the sodium/potassium (UNaK) and aldosterone/renin ratios. We used multivariable generalized linear models to estimate the associations of renin and aldosterone with urine sodium and potassium.

Results: Our cohort was diverse (37% non-Hispanic Black, 14% Hispanic), 66% were male, and median age was 15.3 years; 9% had a secondary etiology and 77% had congenital anomalies of the kidney & urinary tract (CAKUT) or possible initiation of other therapies, like plasmapheresis, on the course of this specific aHUS entity. Our approach would prevent significant cardiovascular sequelae. The identification of somatic and germline mutations will provide further insight into the mechanisms of APA and assist in tailoring appropriate therapy especially in blacks who have high cardiovascular disease morbidity and mortality.

Discussion: Unilateral APA should be considered in any child who presents with drug resistant hypertension and/or hypokalemia as early diagnosis and prompt adrenalectomy would prevent significant cardiovascular sequelae. The identification of somatic and germline mutations will provide further insight into the mechanisms of APA and assist in tailoring appropriate therapy especially in blacks who have high cardiovascular disease morbidity and mortality.

PO2014

Prenatal Nephrology Consultations and Neonatal Dialysis Survey

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Background: Little is known about prenatal nephrology (PN) prenatal consultations for congenital anomalies of the kidney & urinary tract (CAKUT) or possible initiation of kidney replacement therapy (KRT) in neonatal end stage kidney disease (N-ESKD).

Methods: We administered a web-based survey to American Society of Pediatric Nephrology (ASPN) members who reported to the American Society of Pediatric Nephrology listservs. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was adapted from a previously validated instrument and pretested by stakeholders; studied areas related to PN included institutional and personal experience, training and education, and physician confidence. Data were summarized descriptively.

Results: Response rate was 28.7% (29/101). Most respondents were female (79.3%), Caucasian (48.3%), and practiced in an urban setting (85.2%). Only 1 fellow participated in a PC rotation during fellowship, and 46.4% of respondents completed a rotation in medical school or residency. On a scale of 1-5, with 1 being ‘no knowledge’ and 5 being ‘extensive knowledge’ of PC principles, fellows reported a mean knowledge of 2.33 ± 1.04. A single fellow had performed over 10 family meetings to elicit goals of care compared to 64.3% of fellows who had performed over 10 kidney biopsies. A quarter of fellows had never led such a meeting. Confidence in ability to discuss goals of care or address psychological distress in a child with CKD or parent were low, with only 30.8% and 26.9%, respectively, feeling moderately or very confident in their ability. Many fellows (44%) felt low confidence in managing pain in a child with CKD. A desire for additional training was prevalent, with 96.2% of fellows indicating that this training should happen during fellowship.

Conclusions: Few pediatric nephrology fellows receive PC education and experiences during training, resulting in low rates of knowledge and confidence across care domains. Fellows indicate a need and desire for improved PC training.

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (ST32DK07662-30, PI: Hingoranin).
The aims were to evaluate PN practice patterns for prenatal counseling of fetal CAKUT & to describe criteria used by PN to offer KRT in N-ESKD.

Methods: A 35 question Qualtrics® survey was distributed via the North American Pediatric Renal Trials and Collaborative Studies email list between 1/1/2021-3/31/2021. 39 of 108(36%) participating pediatric sites in the US & Canada responded. Median number of faculty (MDs, APPs, APRNs) per center was 7. Median chronic hemodialysis (HD) and peritoneal dialysis (PD) patients per center were 8 & 8, respectively. 38(97%) centers provide prenatal consultation for fetal CAKUT and KRT for N-ESKD. Of those 38 centers, 71% report only a select number of non-trainee workforce members. Only 50% of centers use written/unwritten criteria for decisions about KRT initiation in N-ESKD. Further multi-center research regarding prenatal consultations and neonatal KRT outcomes is necessary to provide greater evidence based practice.

Conclusions: Many PN programs provide prenatal consultations for CAKUT diagnoses by a select group of non-trainee workforce members. Only 50% of centers use written/unwritten criteria for decisions about KRT initiation in N-ESKD. Further multi-center research regarding prenatal consultations and neonatal KRT outcomes is necessary to provide greater evidence based practice.

Table 1: Reported contraindications to dialysis initiation in neonates with ESKD amongst surveyed PN centers (n=38 centers)

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>n=38 Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental refusal</td>
<td>61% (Table 1)</td>
</tr>
<tr>
<td>Birth weight &lt;1500g</td>
<td>52%</td>
</tr>
</tbody>
</table>
| Severe maternal disease | |}

The development of GFR in the first month of life in term born neonates. Black line represents p50, darker blue area indicates p25-p75, lighter blue area indicates p10-p90.

**PO2015**

Postnatal Maturation of Glomerular Filtration Rate in Term Born Neonates: An Individual Patient Data Meta-Analysis

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Background: The evidence from individual studies to support the maturational pattern of measured glomerular filtration rate (GFR) in healthy term born neonates is inconclusive. This hampers the delineation between normal and abnormal kidney development as well as the diagnosis of acute kidney injury (AKI). Thus, we aimed to describe GFR maturation in the first month of life using an individual patient data meta-analysis (IPDMA) of measured GFR data.

Methods: The PubMed and ClinicalTrials.gov databases were searched to identify studies reporting mGFR as measured by exogenous markers or creatinine clearance (CrCl) in healthy term born neonates. Articles were subsequently reviewed by two individual researchers. The relationship between postnatal age and individual clearance values was investigated using restricted cubic splines with generalized additive linear models on individual data, taking into account clustering by study. Data from aggregated studies were used for sensitivity analyses.

Results: 1521 articles were screened and 50 relevant studies reported mGFR in healthy term born neonates. In total, 1055 measured GFR values from 958 neonates were included. Individual patient data (IPD) were available for 371 neonates and 587 neonates were represented by 46 aggregated datapoints as means/medians per cohort. Mean GFR increases rapidly in the first five days after birth from 16.8 (95% CI 11.2-22.5) ml/min/1.73m² at the first day to 39.8 at day 5 (95% CI 35.8-43.7), followed by a more gradual increase to 59.4 (95% CI 45.9-72.9) ml/min/1.73m² at end of the fourth week.

Conclusions: These normative values show a clear developmental pattern of GFR maturation in the first weeks of life and indicate a biphasic increase with the largest increase until day 5. Our IPDMA data can therefore serve as a useful baseline for neonatal GFR.

**PO2016**

Impending Uremic Cardiac Tamponade in an Infant with ESKD


Introduction: Uremic pericarditis (UP) occurs in patients with advanced chronic kidney disease (CKD) prior to dialysis initiation. The incidence of UP is rare due to advances in CKD management by providing adequate and early dialysis. Additionally, it is extremely rare in children. We present a case of a toddler with advanced CKD presenting with UP and impending cardiac tamponade. Daily intensive hemodialysis resulted in a complete resolution of the pericardial effusion.

Case Description: A 2-year-old female presented with a 3-day history of dry cough and low-grade fever. Her medical history was significant for CKD stage 5 related to branchio-oto-renal dysplasia. Her physical examination was remarkable for increased respiratory rate and the presence of pericardial friction rub. A chest radiograph demonstrated enlargement of the cardiac silhouette (Figure 1). An electrocardiogram (ECG) showed sinus rhythm without ST-segment changes and an echocardiogram demonstrated a large circumferential pericardial effusion. The following day, she developed low oxygen saturation and a repeat echocardiogram demonstrated features of early tamponade physiology. Pericardiocentesis was considered but not performed because the amount of apical fluid was deemed insufficient to safely perform the procedure. Daily intensive hemodialysis was initiated and resulted in a complete resolution of the pericardial effusion within a week.

Discussion: Our case of UP in a pediatric patient is exceptionally rare. The most common presentations of this condition are fever, chest pain, and pericardial friction rub. As seen in this case, a characteristic ECG in UP does not show the diffuse ST and T wave elevations often seen in other forms of pericarditis. UP is an absolute indication for dialysis which usually results in rapid resolution of the pericardial effusion.
PO2017

When Less Is More: Phosphate Homeostasis Insights from a Micrillus Inclusion Disease Patient

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Introduction: Micrillus inclusion disease (MVID) is a rare, severe congenital secretory diarrheaea caused by recessive MYO5B or STX3 mutations. Multiple cases of MVID with partial proximal tubule (PT) defects are reported (mostly hypophosphatemia). While MYO5B is expressed in PT cells, MVID patients have normal PT brush border on kidney biopsy, and the PT defect resolves after intestinal transplant. Therefore, it is unlikely that the MYO5B genotype is causally related to the proximal tubulopathy.

Case: A patient diagnosed with MYO5B-MVID, our patient required cyclical total parenteral nutrition (TPN). She was referred to nephrology at age 2 for persistent hypophosphatemia despite escalating TPN phosphate (PO4) content, and nephrocalcinosis. Urinary PO4 wasting was confirmed given the low (<65%) tubular reabsorption of phosphate (TRP). FGF-23 and PTH were elevated. A 24 hr balance study (on/off TPN) revealed that TRP was lowest and FeNa highest (~2%) while on TPN (these values were improved after 6h without TPN). It also confirmed that the negative PO4 balance was only due to renal losses. We hypothesized that high TPN electrolyte concentrations caused an obligate phosphaturic response. Gradual reductions of TPN sodium (Na+) by (13%), then TPN PO4 by (70%) over 4 mo led to normalization of serum PO4 (Figure), TRP (83-91%) and FeNa (~0.3%).

Discussion: We propose that excessive TPN Na+ and PO4 promoted a strong phosphaturic response: the combination of several physiologic factors likely explains this unusual phenomenon. Of interest, the intermittently negative TRP suggest that tubular phosphate secretion must have contributed to the massive phosphaturia. A counterintuitive reduction in TPN Na+ and PO4 reduced renal PO4 wasting without impacting serum Na+. We surmise that other MVID cases of PO4 wasting were also probably due to unusually high TPN electrolyte concentrations. Detailed balance studies are invaluable tools to assess complex fluid/electrolyte disorders.

PO2018

Occurrence of Nephrogenic Systemic Fibrosis with Group II Gadolinium-Based Contrast Agent in a Pediatric Oncology Patient with AKI

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Introduction: Nephrogenic Systemic Fibrosis (NSF) is a rare systemic disorder occurring in patients with chronic kidney disease (CKD) stage IV or V, end-stage renal disease (ESRD), or acute kidney injury (AKI). It is triggered by gadolinium-based contrast agents (GBCAs) and characterized by sclerodermic skin changes from fibrosis and internal organ damage. Almost all NSF cases are associated with group I GBCAs, and only extremely rare, unconfounded cases are reported with group II agent exposure including none in children. We present a case of a female child with acute myelogenous leukemia (AML) in remission and AKI on hemodialysis who presented with NSF six weeks following a magnetic resonance imaging (MRI) with group II GBCA.

Case Description: A 5-year-old female with intermediate risk AML in remission, complicated by prolonged neutropenia with colitis, invasive fungal sinunas and pulmonary infection, and AKI with a renal biopsy-proven acute tubular necrosis on intermittent hemodialysis three times a week presented to the dermatology clinic for evaluation of progressive hardening of her skin. Dermatological examination revealed diffuse, indurated, and compressible plaques involving the lower back, buttocks, posterior thighs, and lateroposterior aspects of the arms. A skin biopsy showed findings consistent with NSF. Six weeks prior to her presentation, she underwent an MRI of the brain and orbits for recurrent disease and received intravenous gadobutrol injection, an IV contrast agent. Treatment with photopheresis twice weekly over a 2-month period resulted in a gradual improvement of her condition.

Discussion: Our case of group II GBCAs induced NSF is exceptionally rare, with no prior publications from our group. Despite IV GBCAs exposure reported to date. While NSF has been reported rarely in children who received group I GBCAs, the risk of NSF in children exposed to group II or even group III GBCAs is unknown. We strongly recommend that physicians continue kidney function screening prior to group II GBCAs administration in children and carefully evaluate the risk versus benefit of using or withholding group II GBCAs for clinically indicated MRIs in patients with CKD stage IV/V, ESRD, or AKI.

PO2019

Exploring Population Pharmacokinetic Models in Patients Treated with Vancomycin During Continuous Venovenous Hemodiafiltration (CVVHDF) on Different Anticoagulant Modalities

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Background: Treatment with photopheresis twice weekly over a 2-month period resulted in a gradual improvement of her condition.

Methods: We conducted an exploratory population pharmacokinetic (PK) analysis in our tertiary level intensive care unit (ICU) on PK of vancomycin following intermittent infusion in critically ill patients receiving continuous venovenous haemodiafiltration (CVVHDF). Clinical, laboratory and dialysis data were extracted from the electronic healthcare record (EHR) using strict inclusion criteria. A population PK analysis was conducted with a one compartment model using the Pmetrics population PK modelling package. A base structural model was developed and further analyses were performed with and without covariate data, including regional citrate anti-coagulation (CIA) vs non-CIA, to improve model prediction through covariate inclusion. The final selected model simulated patient concentrations using probability of target attainment (PTA) plots to investigate the probability of different dosing regimens achieving target therapeutic concentrations.

Results: 107 vancomycin dosing intervals (155 levels) in 24 patients were examined. An acceptable base model was produced (Plots of observed vs. predicted concentrations (Obs-Pred) R²=0.78). No continuous covariates explored resulted in a clear improvement over the base model. Use of anti-coagulation modality and vasoressor use as categorical covariates resulted in similar PK parameter estimates, with a trend towards lower parameter estimate variability both with use of CIA and without vasoressor use. Simulations using PTA plots suggested that a 2 g vancomycin loading dose followed by 750 mg 12 hourly as a maintenance dose, commencing 12 hours after loading, is required to achieve adequate early target trough concentrations of at least 15 mg/L.

Conclusions: Using robust EHR data to construct a base model from a population known to have highly heterogeneous antimicrobial PK, simulations based on PTA plots showed that we could achieve acceptable trough vancomycin concentrations early in treatment with a 2 g loading dose and a maintenance dose of 750 mg 12 hourly for ICU patients on CVVHDF.

PO2020

Evaluation of Gabapentinoid Dosing and Adverse Events in Patients with Advanced CKD

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Background: Gabapentinoids (GP, gabapentin and pregabalin) are frequently prescribed in individuals with chronic kidney disease (CKD); however, their exclusive renal elimination warrants dose adjustments to decrease the risk of toxicity. Data to describe prescribing patterns and incidence of adverse events in advanced CKD is limited. This study evaluated prescribing patterns for GPs and whether excessive dosing was associated with increased incidence of gabapentinoid-related adverse events (GRAEs).

Methods: A retrospective analysis of adult patients admitted to the Methodist LeBonheur Healthcare system from January 2014 – October 2020 with CKD stage 4, 5, or end-stage kidney disease (ESKD) receiving GPs prior to admission or during hospitalization for at least two days was conducted. Patients were grouped based on whether the average daily dose prescribed was higher than recommended (inappropriately dosed, (ID)) or as recommended (appropriately dosed (AD)) for CKD stage. The occurrence of GRAEs was assessed in patients with chronic kidney disease (CKD) vs non-CKD, to explore the incidence of adverse events in patients with advanced CKD.

Results: The 200 patients included were predominantly female (51%), black (72%), CKD 5/ESKD (84%) with a mean age 61±14 years, and prescribed gabapentin (90%) with 111 (55%) in the AD group and 89 (45%) in the ID group. Baseline characteristics were similar between groups except type 2 diabetes and nephropathy were more common in the ID group. For the primary outcome, there was no statistically significant difference in GRAE (18% vs. 19%, p=0.84). GRAEs were associated with older age (mean age 65±11 years for GRAEs vs. 60±14 years for no GRAE; p=0.001) and seizure history (14% for GRAEs vs. 0% for no GRAE; p=0.02), but not with CKD severity. LOS was significantly longer for patients who experienced a GRAE than for those who did not (8.5 ± 3.3 days; p=0.04).

Conclusions: In patients with advanced CKD, appropriate dosing of gabapentinoids is important to minimize the risk of adverse events, particularly in patients of older age or with a history of seizures. There is a need for prescriber education given the high frequency of inappropriate gabapentinoid dosing in patients with advanced kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2021

Chronic Dosing of Voclosporin at Clinically Relevant Exposure Levels Does Not Induce Renal Fibrosis Markers in Rats

Background: Although prognosis of lupus nephritis (LN) has improved, the long-term outcome is still poor, with many patients progressing to end-stage renal disease. Calcineurin inhibitors (CNIs) like cyclosporine A (CsA) and tacrolimus have demonstrated benefits in LN; however, prolonged use is associated with renal fibrosis. CsA-induced fibrosis has largely been in the context of high doses required for immunosuppression in transplant patients. Voclosporin (VCS), a potent, novel CNI with a predictable PK/PD profile, is approved for treatment of LN. This study tested the hypothesis that the clinically effective dose of VCS used in LN patients, would not induce fibrosis markers in the chronic dosing rat model compared to CsA and vehicle controls.

Methods: Sprague Dawley rats (n=10/group) on a low sodium (0.05%) diet were treated by oral gavage (QD) with VCS (4 mg/kg), cyclosporine A control (10 mg/kg) or vehicle control (5 mL/kg) for 3 or 6 weeks. Clinical chemistry was performed on serum, and overnight urine. Gene expression (RT-qPCR) and histology were performed on kidneys. Data were analyzed as change from baseline.

Results: There were no significant differences in clinical measures of renal or liver function. There were no significant changes in urine protein/creatinine or fractional excretion. Serum total bilirubin and cholesterol were significantly increased in the CsA treated group compared to vehicle and VCS. At 3 weeks, there was a significant decrease in expression of Tgfβ1 and the epithelial-mesenchymal transition (EMT) marker Cdh2 (N-cadherin) in VCS treated animals compared to vehicle and CsA, and significant decreases in expression of the EMT regulators, Snail (SNA1) and Sna2 (SLUG), and the extracellular matrix components (ECM) Col1a1, Col3a1 and Vim in the VCS treated group. At 6 weeks, trends between groups remained, and there were significant decreases in Tgfβ2 and Col3a1 in the VCS treated group. At 6 weeks, there were no differences in renal histopathology.

Conclusions: This study shows that the clinically relevant dose of voclosporin does not induce renal fibrosis markers in rats, in contrast to the CsA control. Additionally, voclosporin may protect against renal EMT and fibrosis progression, which is associated with CsA. Collection of data from a two-year continuation renal biopsy sub-study of AURORA-1 is ongoing.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

PO2022

The Effect on Renal Function of Patients on HIV Pre-Exposure Prophylaxis (PrEP)
Alfredo B. Tru,1,2 David J. Looney,1,2 VA San Diego Healthcare System, San Diego, CA,1 University of California San Diego, La Jolla, CA,2

Background: Tenofovir, a nucleotide reverse transcriptase inhibitor, is used in management of hepatitis B and as part of a highly active antiretroviral medication regiments for HIV infected individuals. Tenofovir disoproxil fumarate (TDF) is one of two tenofovir nucleotide analog. The U.S. Food and Drug Administration (FDA) recommended on 16 July 2012 the use of tenofovir-emtricitabine combination medication as pre-exposure prophylaxis (PrEP) against HIV. TDF is cleared through glomerular filtration and tubular secretion. Its nephrotoxicity includes renal tubular acidosis type 2, acute tubular necrosis, and tubulointerstitial disease. Reported data regarding effect of renal function from tenofovir based PrEP are less than 24 months of follow-up. This study evaluates the effect on renal function in patients receiving TDF for PrEP over more than 24 months because it can affect the future of PrEP with more expensive analog of tenofovir (TAF) promoted as less nephrotoxic and other PrEP medications.

Methods: VA San Diego database on adults receiving PrEP is the source for this data. Serum creatinine and estimated glomerular filtration rate (eGFR) are obtained as part of PrePrEP protocol which started in 2014. The PrePrEP protocol follows the Centers for Disease Control and Prevention (CDC) recommendations of pre-initiation serum creatinine and eGFR then 3 months after the initiation and annually thereafter. Acute kidney injury is define as an increase in serum creatinine by >0.3 mg/DL within 48 hours or increase in serum creatinine to >1.5 times baseline based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines which is the most recent preferred definition and used more consistently in clinical studies (1,2).

Results: Since 2014, 103 individuals are in the PrePrEP program. At one year, there are 87 patients and none meets the criteria for AKI. After 2 years, there are 73 patients and 2 meet the criteria of AKI. Their kidney function returned back to baseline one month later. 55 individuals completed 3 years on PrEP and none meets the criteria for AKI. 41 individuals completed 4 years of PrEP and none meets criteria for AKI. The average change of eGFR at one year is 7.1%, 7.5% at 2 years, 8.6% at 3 years and 8.1% at 4 years.

Conclusions: Serum creatinine is stable on PrEP and none meet KDIGO AKI definition. The decrease in eGFR is not significant to warrant a change of TDF based PrEP.

PO2023

Tenofovir Kidney Clearance Predicted by Glomerular and Tubular Secretory Functions

Background: Proximal tubular secretion is the primary kidney mechanism for eliminating most prescribed medications. Yet, kidney drug dosing is based on estimates of the glomerular filtration rate (GFR). In an empiric pharmacokinetic study, we compared the spectroscopy measurements of endogenous secretory solutes. We used linear regression, leave one out cross-validation, root mean squared error, and mean percentage error to describe agreement between kidney functions and TDF clearance.

Methods: We recruited 27 adult patients across a wide range of kidney function. Exclusion criteria were use of tenofovir or a secretory antagonist (cimetidine, digoxin, probenecid), dialysis, nephrotic syndrome, or cirrhosis. We administered a single 125mg oral dose of TDF and estimated its kidney clearance from the area under the plasma time concentration curve and urine drug recovery. We measured GFR by iohexol clearance (iGFR) and estimated secretory function from a 10-hour urine collection with mass-spectroscopy measurements of endogenous secretory solutes. We used linear regression, leave one out cross-validation, root mean squared error, and mean percentage error to describe agreement between kidney functions and TDF clearance.

Results: Mean age of the study population was 55 ±15 years, 63% were male, and median GFR was 78 ml/min/1.73m² (IQR 52, 99 ml/min/1.73m²), ten participants (37%) had an iGFR <60 ml/min/1.73m². The mean percentage error (MPE) between observed and iGFR-predicted TDF kidney clearance was 26.7% (Table). The clearances of four endogenous secretory solutes improved the prediction of TDF clearance beyond that of GFR, cinnamoylglycine, indoxyl sulfate, isovalerylglycine, and tiglylglycine. Combining solute clearance and iGFR results in a lower overall mean percentage error in TDF kidney clearance prediction.

Conclusions: Measurements of secretory solute clearance represent a potential future strategy for improving kidney drug dosing.

Funding: NIDDK Support
trajectory of IgA suppression as that achieved by the IV formulation in healthy volunteers, in which a single dose of the intravenously administered IgA by approximately 50% from baseline values at 8 weeks post-dose (Figure 1).

Conclusions: Preliminary results of this Ph1 study of SC-administered VSY6649 demonstrated acceptable safety, tolerability, and bioavailability, and suppressed total IgA by approximately 50-55% from baseline, comparable to IV doses.

Funding: Commercial Support - Visterra Inc, Otsuka Pharmaceuticals Inc

Figure 1. Total IgA Mean Percent Suppression From Baseline Following Single Dose VSY6649 Administered Via SC or IV Route

PO2025

Association of Oxyipurin Exposure with Progression of CKD: Pre-Specified Substudy Results from the CKD-FIX Trial

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Background: The CKD-FIX trial evaluated the effect of allopurinol on eGFR slope over 104 weeks in patients with chronic kidney disease (CKD) and risk of progression. The aim of this pre-specified sub-study was to assess whether exposure to oxypurinol, the active metabolite of allopurinol, predicts change in eGFR.

Methods: Adults with CKD stage 3 or 4 (n=369), no history of gout, and high risk of progression (urinary albumin-to-creatinine ratio ≥265 mg/g or eGFR decrease ≥3.0 mL/min/1.73 m² in the preceding year) were randomized to receive allopurinol (n=245) or placebo (n=124). Plasma oxypurinol concentrations were determined at weeks 16, 24, 40, 56, 72, 88 and 104 post-initiation of allopurinol. Non-compartmental pharmacokinetic analysis of oxyipurinol concentrations was performed to determine oxypurinol exposure (area under the concentration time curve) using the Simbiology module of MATLAB. The association between eGFR slope and oxypurinol exposure was assessed using least-squares estimates linear regression.

Results: Overall 155 (84%) patients (mean eGFR 31.7 mL/min/1.73 m², mean serum urate 8.0 mg/dL) received allopurinol and had a plasma oxypurinol concentration available. At the end of the 12-week dose-escalation phase, the majority of patients (123; 79%) were prescribed allopurinol 300 mg and the remainder 100 mg (13%; 8%) or 200 mg (19; 12%). The mean (standard deviation) eGFR slope and reduction in serum urate concentration were -3.32 (5.02) mL/min/1.73 m²/year and 2.6 (0.14) mg/dL, respectively. Based on a total of 819 plasma oxypurinol concentrations (median n=6 per patient), there was no correlation between eGFR slope and total oxypurinol exposure (P=0.93), including after adjusting for allopurinol dose (P=0.99). These results were consistent across the three allopurinol dosing regimens. Greater oxypurinol exposure was associated with larger reduction in serum urate concentrations (P<0.0001).

Conclusions: In CKD-FIX participants, exposure to oxypurinol was not associated with change in eGFR. However, reduction in serum urate concentration was dependent on plasma oxypurinol exposure.

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

PO2026


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Background: High urinary oxalate levels (UOx) in patients with enteric hyperoxaluria (EH) can lead to recurrent kidney stones, nephrolithiasis and chronic kidney disease. SYN8802 is an engineered E. coli Nissle 1917 that contains an oxalate degrading pathway which converts oxalate to formate within the gastrointestinal (GI) tract, thereby reducing the risk of renal stone disease. Part A of this proof-of-concept study was conducted in healthy volunteers (HV) and Part B in Roux-en-Y (RYGB) patients with hyperoxaluria.

Methods: In Part A, a well-tolerated dose of 3e11 live cells/dose was identified in HV. At this dose, the percent change from baseline UOx levels was -28.6% (90% CI: -42.4 to -11.6) compared to placebo in diet-induced hyperoxaluria. This dose is being studied in Roux-en-Y patients with hyperoxaluria in Part B. The results from the RYGB population will be reported.

Conclusions: These results provide proof of mechanism for UOx lowering by GI consumption of oxalate in diet-induced hyperoxaluria. Part B seeks proof-of-concept in patients with enteric hyperoxaluria.

Funding: Commercial Support - Synlogic Inc.

PO2027

Tacrolimus Induces Ligand-Independent TGF-β Receptor Signaling to Promote Renal Fibrosis

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Background: Although calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporin A dramatically improved the quality of patient care, long-term therapy carries irreversible damage to the kidneys in the form of renal fibrosis. These morphologic changes ultimately lead to a decline in renal function and can progress to end-stage renal failure. These detrimental outcomes present a critical need to identify innovative therapeutic mechanisms by which CNIs cause renal damage. It is well established that TGFβ is a major contributor to CNI-induced renal fibrosis. However, the underlying mechanisms remain unknown. The objectives of this study are to 1) investigate whether TGFβ secretion is required to stimulate TGFβ receptor signaling in a model of CNI-induced renal fibrosis and 2) investigate whether calcineurin plays a critical role in regulating TGFβ receptor activity.

Methods: To examine the role of calcineurin inhibition in altered TGFβ receptor signaling, wild type mice were treated with either vehicle (100% ethanol) or 10 mg/kg tacrolimus for 7 days. To confirm in vivo findings, wild-type mouse renal cortical fibroblasts were treated with either vehicle (100% ethanol) or 1μM tacrolimus for 24 hours in the presence and absence of anti-TGFβ neutralizing antibodies. TGFβ receptor expression and activation, TGFβ receptor downstream signaling mediators, profibrotic markers and calcineurin activity were analyzed.

Results: Findings demonstrated that CNI-induced loss of calcineurin activity is accompanied with enhanced TGFβ receptor activation and signaling. Notably, increasing concentrations of anti-TGFβ neutralizing antibodies failed to abolish aberrant TGFβ signaling and increased expression of profibrotic markers.

Conclusions: Together, these results demonstrate that 1) CNIs promote ligand-independent TGFβ signaling and 2) calcineurin plays a functional role in regulating TGFβ receptor activity.

Funding: NIDDK Support, Other U.S. Government Support

PO2028

Immunoreactivity of CD3+CD4+ in Stable Young, Middle Aged, and Elderly Kidney Transplant Recipients Receiving Maintenance Tacrolimus and Mycophenolic Acid Immunosuppression

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Background: Tacrolimus and mycophenolic acid are the standard of care in most stable kidney transplant recipients (KTR) at U.S. transplant centers. However, there are limited data that determine within subject immunophenotypic responses over the adult age range. This study examined ex vivo immunoreactivity of CD3+CD4+ lymphocytes in stable young, middle age and elderly KTR receiving tacrolimus and mycophenolic acid.

Methods: Fifteen stable KTR greater than 1 yr post-transplant completed a 12-hour study with serial collections at pre-dose (trough-0 hr), 4, 8 and 12 hours. The immune response measurement was evaluated by Interferon-2 (IL-2) and TGF beta-1 production by CD3+CD4+ T cells after ex-vivo treatment with PMA/Ionomycin with Brefeldin-A. Data was represented as within individual, timed collection and the mean for all time points of ex-vivo stimulation by cell sub-populations stratified by young, middle age and elderly. Comparisons were made using Kruskal-Wallis test.

Results: Table summarizes the major findings. There were no group differences between tacrolimus and mycophenolic acid troughs with all tacrolimus troughs within the therapeutic range. Increased IFNγ from CD3+CD4+ T cells was quantitated by ex vivo immunoreactivity in middle age recipient at the 4 and 8 hours during the 12-hour study period. No significant differences were noted for interleukin-2 quantitated from CD3+CD4+.

Conclusions: These data indicate increased IFNγ from CD3+CD4+ T cells for ex vivo immunoreactivity over a 12-hour dosing interval in young middle age KTR receiving long-term maintenance immunosuppression. Variable immunodynamics and the implications of intra- and interpatient variability in immunoreactivity across the range of adult KTR require further investigation of clinical and allograft outcomes.

Funding: Other NIH Support - National Institute of Aging

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Urinary Proteomics and Effects of Dapagliflozin Treatment in Persons with Type 2 Diabetes and Kidney Disease

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Background: About 40% of persons with type 1 (T1D) or type 2 diabetes (T2D) develop diabetic kidney disease (DKD) posing a major economic burden on health care systems. Sodium Glucose Co Transporter 2 inhibitors (SGLT2i) have emerged as a novel treatment option for T2D and DKD. Although the kidney-protective effects of SGLT2i are well documented, the mechanisms remain unclear. The current study aims to investigate SGLT2i function through urinary proteomics.

Methods: A double-blinded, randomized, placebo-controlled, crossover trial comprising 36 persons with T2D was treated with 10 mg of dapagliflozin for 12 weeks or matching portion of placebo on top of their standard diabetes treatment at the Steno Diabetes Center Copenhagen, Gentofte, Denmark. All participants had albuminuria (UACR > 300 mg/g) and received RAAS medication. Clinical factors like BMI blood pressure (BP), estimated glomerular filtration rate (eGFR), LDL, and HDL cholesterol, were measured at baseline, and after trial. Changes in clinical factors were modelled using linear mixed effects model adjusting for relevant clinical covariates. Urinary proteomics data in pre and post treatment groups (n=32) were analysed using paired Mann Whitney U test. Multiple testing correction was performed and p < 0.05 was considered significant. We further verified whether identified peptide levels differed significantly between T1D DKD vs. healthy controls (n=210) and performed pathway enrichment analysis with STRING database.

Results: Trial participants had a mean (SD) age of 63 (8) years, 88% males, diabetes duration 15.9 (4.7) years, BMI 33.7 (5.4) kg/m², Hba1c 8.8 (1.2)% median (IQR) UACR 154 (94–329), eGFR 85.5(19.1) ml/min/m², respectively. 19 proteins significantly changed after treatment. Type I and III collagen (α1, II), (III), and (I) chains, α-2HS-glycoprotein, and polymimic immunoglobulin receptor proteins increased while albumin, α1–antitrypsin, and α1B–glycoprotein decreased multifold. This was reflected in the DKD-control cohort.

Conclusions: We identified differential urinary peptide patterns in response to SGLT2i (Dapagliflozin) treatment on individuals with T2D and DKD. Extracellular matrix organization, inflammation, coagulation, renal fibrosis, and wound healing pathways were enriched. We suggest the involvement of expected and novel proteins.

PO2030

Antifibrotic Effects of Low-Dose SGLT-2 Inhibition in Comparison to Standard Angiotensin II Receptor Blockade in 5/6 Nephrectomised Rats

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Background: The proposed project comprises of the development of a kidney proximal tubule (KPT) microphysiological system (MPS) from human cells as well as two experimental animal species that are typically used in kidney toxicity screening: rat and dog. These KPT-MPS may serve as a new important tool in chemical toxicity screening, allowing cross-referencing animal-based MPS data within vivoanimal data and with human-based MPS data and clinical outcomes. It also has the potential to result in a significant reduction of the use of live animals in studies.

Methods: The Nortis chip is made from silicone in a polycarbonate casing and is designed to use the “mandrel” method for generating channels within a 3D extracellular matrix using retractable small glass fibers. The fibers serve as starting points for growing tubular tissue structures, such as vessels or kidney tubules. The chip is compatible with high-quality imaging, tissue sampling, and up- and down-stream fluid collection. Multiple publications have documented the suitability of the Nortis system to generate functional human KPTs and how well they resemble the function of in vivo tubules. All 3D MPS experiments were accompanied by 2D controls for comparison, using a traditional culture dish system. To assess viability of tissue, Live-Dead staining assays were run on canine tubules with Calcein (live) and the nucleic acid stain ethidium homodimer I (dead), the results of which indicated sufficiently viable tubules. Confocal imaging and 3D rendering of these tubules demonstrates presence of key ion and drug transport proteins in their respective basolateral and luminal domains.

Results: Preliminary studies have shown that rat and canine derived KPT-MPS in the Nortis platform produce structurally viable tissue structures that elicit injury markers in response to nephrotoxic insults using in vivo relevant toxic compounds in a differential manner.

Conclusions: Our preliminary data suggests that Nortis kidney chip allows for an ideal predictive platform for comparative toxicity studies, allowing for fast and highly predictive preclinical simulations.

Funding: Other NIH Support - NCATS

PO2031

HIF Prolyl-4-Hydroxylase Inhibitor AKBX27922 Induces Cellular Metabolic Adaptation

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Background: Inhibition of prolyl-4-hydroxylase (PHD) enzymes leads to the stabilization of hypoxia inducible factor (HIF) and the expression of HIF target genes. Because of effects on erythropoiesis, several PHD inhibitors are undergoing clinical evaluation for the treatment of anemia with chronic kidney disease. However, the impact on other biological functions is not well investigated. We demonstrate that AKBX27922, a novel small molecule PHD inhibitor, can shift cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis, mimicking adaptation to hypoxia.

Methods: Inhibition of PHD enzymatic activity was determined using the time-resolved fluorescence resonance energy transfer assay. HIF 1α stabilization in Hep3B cells was measured by meso scale discovery technology and protein expression of HIF target genes by enzyme linked immunosorbent assay. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured in HepG2 cells with the Seahorse technology. Pharmacodynamics of the inhibition were confirmed in vivo.

Results: In vitro, AKBX27922 potently and in a concentration-dependent manner, and without chelating iron, inhibited PHD1 and PHD2 enzyme activity, leading to HIF 1α stabilization and expression of HIF target genes implicated in erythropoiesis, angiogenesis, and cell survival. Pretreatment of HepG2 cells with AKBX27922 dose-dependently reduced both basal and maximal OCR without affecting cellular viability, while ECAR was significantly increased. Reactive oxygen species production in human primary renal epithelial cells was decreased. In vivo, AKBX27922 stabilized HIF in the liver and kidneys, as measured by luciferase activity in the oxygen-dependent degradation domain (ODD)-luciferase reporter mouse. In rats, AKBX27922 induced time-dependent stabilization of HIF1α in the kidney medulla and papilla, and increased expression of glycolysis related (ALDOC, CAR9, PDK1, PFKFB4, LDH1) and other HIF target genes (EPO, ADM, HMOX-1) in the kidneys and liver.

Conclusions: PHD inhibitor AKBX27922 mimics hypoxia, leading to HIF-driven metabolic adaptation. This novel small molecule will be useful as an in vitro and in vivo research tool for additional mechanistic studies that probe the pletotropic biology of HIF.

Funding: Commercial Support - Akebia Therapeutics, Inc.
PO2033
Forced Saline Diuresis Successfully Treats Lithium Intoxication
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Background: Forced 0.9% normal saline (NS) diuresis (FSD) is not advised by poison control centers for lithium intoxication (LI) but in papers ≥ 71 & ≥ 78 showed ≥ 350 - 500 mL/hr of FSD treated LI at ≥4mEq/L successfully. We studied all pts with LI over 10 years with both acute (A) overdoses and chronic (C) LI to compare FSD in both groups to pts requiring hemodialysis (HD).

Methods: We found ≥20 LI pts seen over 10 years. Our team uses NS at ≥200-500 mL/hr as FSD in pts w/o CHF. 9 pts had Acute overdoses of L & ≥4 C LI due to reduced gift, ACE drugs or NSAIDs. These 14 got FSD, 200-500 mL/hr until L was < 1 mEq/L. 6 pts needed HD due to severe toxicity (seizures, coma, hypothension). We compared & showed the mean ±SEM values for peak L mEq/L, GFR calculated by the Cockcroft-Gault equation, the rate of L decrease in mEq/hr, the normalized rate of L decrease in mEq/24 hr & time in hrs to reach a L level of 1.0 mEq/L amongst the 3 groups.

Results: The mean peak L levels were: FSD ALI, 2.8 ± 0.2 (range, 2.3-4), FSD C LI, 2.8 ± 0.4 (range, 2.4-2), HD LI 3.5 ± 0.4 (range, 1.8-4). There were no differences in L levels in the mean. The mean GFR was: FSD ALI, 127 ± 17, FSD C LI, 60 ± 17, HD LI 142 ± 7, p < 0.05. The normalized rate of L decrease was: FSD ALI vs FSD C LI, 0.05 ± 0.1, HD LI, 0.22 ± 0.4. There was no difference in the rate of L decrease in FSD A LI & HD LI but both were much faster than FSD C LI, p < 0.05. The mean 24 hour decrease (mEq/L) in L was: FSD A LI, 3.1 ± 2.2, FSD C LI, 1.1 ± 0.2, H DLI, 5.5 ± 1.6. p < 0.05 FSD LI vs FSD A LI or HD LI. The time to L level of 1.0 mEq/L was: FSD A LI, 14 ± 1.3 h, FSD C LI, 36 ± 4.3 h, HD LI, 11.5 ± 2.3 h due to rebound after HD. There was no difference in the time to normal L between FSD A LI & HD both were much faster than FSD C LI. Linear regression of the rate of L decrease compared to the hourly rate of NS in HD LI pts showed greater decreases in L level with greater rates of FSD, r = −82, p < 0.006. No pt had a serum Na > 145 mEq/L.

Conclusions: FSD with NS at rates of ≥200-500 mL successfully treats A LI and rates of L decrease in patients approaching HD for LI C LI can be treated with FSD but the rates of L decrease are slower possibly due to lower GFRs in these pts. This is the first study in 40 years showing efficacy of FSD in LI.

Funding: Clinical Revenue Support

PO2034
Snow White and the Apple: When Drugs Become Poisons
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Introduction: Commonly used drugs can cause significant toxicity in unfavorable clinical scenarios. We present a case of a pregnant female on a high dose of baclofen which led to significant neurotoxicity as her GFR dropped during an episode of acute pancreatitis

Case Description: A 29-year-old pregnant Caucasian Female presented to an OSH with abdominal pain of a day’s duration. She was obese and had DM-II, hypertension as well as H O a brain tumor treated when she was 10 years old. She was 29 weeks pregnant. Abdominal pain was sharp, epigastric and radiating to her back with nausea and vomiting. She was found to have severe acute pancreatitis. Her kidney function was normal (creatinine 0.5 mg/dl) on admission but on hospital day 2 it rose to 1.5 mg/dl and was at 2.3 mg/dl the next day. On hospital day #2 she became obtunded without response to naloxone and flumazenil. She was transferred to our hospital. She was comatose with minimal movement on sternal rub. Her neck was supple without obvious cranial nerve lesions. MRI of the brain revealed prior (L) frontal craniotomy, post-surgical glosis and encephalomalacia, stigmata of her brain surgery. EGG suggested encephalopathy but no active seizures. A review of medicines at OSH revealed baclofen 20 mg TID scheduled for 40 years showing efficacy of FSD in LI.

Funding: Veterans Affairs Support, Private Foundation Support

PO2035
Efficacy of Pi-Binder Lanthanum Carbonate in Reversing Systemic Effects of a High-Phosphate Diet in Mice
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Background: Modulating dietary inorganic phosphorus (P) is particularly important for patients suffering from chronic kidney disease (CKD) as excess P consumption and subsequent elevated serum P levels can lead to significant health problems, including increased mortality. Recent data now suggests that high P consumption might also have negative health consequences even in those with clinically normal renal function. The predominant clinical therapy to reduce serum P and related health complications of CKD patients is orally administered P-binders with meals, including the commonly used Lanthanum Carbonate (LaC). Our study assessed the strategy of binding P in the gut to reduce health consequences of a high P diet including changes in bone volume, P-responsive circulating factors, and gene expression in the kidney.

Methods: Healthy 10-Week-old, female C57BL/6J mice were fed diets with varying P for 5 weeks. Low P (LPD, 0.2% P), Normal P (NP, 0.6% P), High P (HPD, 1.8% P), and HPD supplemented with LaC (3%). All diets contained 0.6% Calcium, similar protein, Kcal, and fat%. Circulating P-responsive factors (FGF23, OPN) were measured by ELISA, bone volume by micro-computed tomography, and gene expression in the kidney by quantitative real-time (qRT) PCR.

Results: HPD resulted in increased serum FGF23 and OPN, decreased bone volume (trabecular, cortical), and significant changes in kidney gene expression of inflammatory protein Lecl, P responsive Klotho, vitamin D synthesis Cyp27b1, and Pi-transporter NaPi2b. HPD-induced increases in serum OPN and Cyp27b1 were partially reversed gene expression changes in the kidney but did not alter HPD-induced bone loss. Conclusions: The clinically used P-binder LaC only reversed certain HPD-induced consequences, suggesting a multifactorial mechanism, and therefore may require a therapeutic strategy beyond reducing gut P-absorption. Decreasing P consumption was substantially more effective at minimizing physiological repercussions like bone loss. Changes in kidney gene expression after a sustained HPD also reveal potential long-term consequences on kidney health/function in otherwise healthy individuals. Given divergent claims concerning LaC binder efficacy, our study shows LaC corrects some but not all—effects of a high P diet.

Funding: Clinical Pharmacology, Pharmacokinetics, and Drug Toxicity in Kidney Diseases

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2037
Combination Therapy of Neprilysin Inhibitor with AT2R Agonist C21 Provides Superior Renoprotection Compared to Its Combination with AT1R Antagonist Valsartan in High-Sodium Diet-Fed Obese Zucker Rats
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Background: The neprilysin (NEP) inhibitor sacubitril (SAC) combined with the angiotensin II type 1 receptor (AT1R) blocker valsartan (VAL) (i.e. Entresto) is clinically approved for the treatment of heart failure (HF) associated with reduced ejection fraction, owing mainly to its ability to preserve atrial natriuretic peptide (ANP), a substrate of NEP. However, many HF patients treated with Entresto have presented with increased albuminuria. We have reported that the agonist of angiotensin II type 2 receptor (AT2R) Compound 21 (C21) prevents proteinuria and is renoprotective in obese Zucker rats (OZR) fed high sodium diet (HSD). Thus, we hypothesized that SAC/C21 combination provides superior renoprotection compared to the current SAC/VAL therapy.

Methods: Male OZR 10-11 wks. old were treated daily via oral gavage with vehicle, SAC (10mg/kg/day) + VAL (10mg/kg/day) while fed HSD (4%) for 16 days.

Results: Untreated HSD-fed OZR showed reduced plasma ANP and increases in renal cortical Ang II (all p<0.05 vs OZR-fed 0.4% normal sodium diet (NSD)). These changes were associated with a modest increase in kidney weight and kidney dysfunction, evident by increased proteinuria, and reduced urinary excretion of urea nitrogen and creatinine (all p<0.05 vs OZR-fed NSD). Other indices of renal injury include increased cortical expression of nephrin (p<0.05 vs OZR-fed NSD), podocin, megalin, albuminuria, and increased urinary osteopontin (OPN). Treatment with SAC/C21 significantly prevented increases in renal Ang II, proteinuria, albuminuria, nephrin expression and kidney weight (all p<0.05 vs OZR-fed HSD), while SAC/VAL did not affect these parameters. Furthermore, SAC/C21 prevented the decline in the excretion of urinary creatinine and decreased urinary OPN (all p<0.05 vs SAC/VAL). Moreover, SAC/VAL therapy increased plasma renin concentrations ~3-fold compared to OZR-fed HSD and SAC/C21.

Conclusions: Together, this study suggests that combination therapy with SAC/C21 afforded superior renoprotection compared to SAC/VAL therapy in HSD-fed OZR.

Funding: NIDDK Support

PO2038
Is Basal Nitric Oxide Activity of the Renal Vasculature Altered? Analysis of a Randomized Controlled Trial Comparing Two Combination Therapies
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Background: Recently we demonstrated that a combination therapy with empagliflozin and linagliptin in patients with type 2 diabetes mellitus(T2DM) induce changes in renal hemodynamics. The purpose of this study was to analyze the influence of basal nitric oxide(NO) activity of the renal vasculature on the described changes of the renal hemodynamic profile.

Methods: In this study patients with T2DM were randomized to receive either empagliflozin and linagliptin(E+L group, n=50) or metformin and insulin glargine(M+I group, n=46), for 3 months. Renal hemodynamics were assessed with constant-infusion protocols according to the model established by Gomez. The basal NO activity in the renal circulation has been assessed by established by Gomez. The basal NO activity in the renal circulation has been assessed by

Results: Urinary Cell mRNA Profile Diagnosis of Borderline T Cell-Mediated Rejection in Kidney Allografts
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Background: Borderline rejection (BR) is associated with inferior outcomes. In CTOT-04, we discovered and validated a urinary-cell signature of CD3ε mRNA, IP-10 mRNAs, and 18s rRNA diagnostic of TCMR (Suthanthiran et al. N Engl J Med, 2013). We investigated whether this signature is diagnostic of BR.

Methods: Urinary cell mRNAs measured in 377 biopsy-matched urine samples from 300 kidney transplant recipients. Interstitial inflammation (i) and tubulitis (t) scored by Banff criteria. Diagnosis of BR=i1,t1, i2,t1, or i1,t2 and TCMR= i3, t3.

Results: 293 biopsies included (Table 1). CTOT-04 signature distinguished i0,t0 from BR and TCMR(p<0.0001,ANOVA)(Fig.1A).18S normalized CD3ε and IP-10 mRNAs elevated in BR and TCMR urine(Fig.1D-E). Other indices of renal injury include increased cortical Ang II, proteinuria, and reduced urinary excretion of urea nitrogen and creatinine (all p<0.05 vs OZR-fed 0.4% normal sodium diet (NSD)). These changes were associated with a modest increase in kidney weight and kidney dysfunction, evident by increased proteinuria, and reduced urinary excretion of urea nitrogen and creatinine (all p<0.05 vs OZR-fed NSD). Other indices of renal injury include increased cortical expression of nephrin (p<0.05 vs OZR-fed NSD), podocin, megalin, albuminuria, and increased urinary osteopontin (OPN). Treatment with SAC/C21 significantly prevented increases in renal Ang II, proteinuria, albuminuria, nephrin expression and kidney weight (all p<0.05 vs OZR-fed HSD), while SAC/VAL did not affect these parameters. Furthermore, SAC/C21 prevented the decline in the excretion of urinary creatinine and decreased urinary OPN (all p<0.05 vs SAC/VAL). Moreover, SAC/VAL therapy increased plasma renin concentrations ~3-fold compared to OZR-fed HSD and SAC/C21.

Conclusions: Together, this study suggests that combination therapy with SAC/C21 afforded superior renoprotection compared to SAC/VAL therapy in HSD-fed OZR.

Funding: NIDDK Support
Preserved Kidney Allograft Function and Unique Urinary Biomarker Profiles in Living Donor Kidney Transplant (LDKT) Patients Tolerated with an Investigational Allo-Hematopoietic Stem Cell Transplantation Therapy

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Background: We previously reported that 37 patients were transplanted in an open-label, single-arm phase 2 protocol to induce immune tolerance in LDKT recipients.

Methods: The protocol was based on tolerogenic CD8+/TCR+ facilitating cells (FCR001), nonmyeloblastic conditioning and enrollment agnostic to the degree of HLA mismatch. Tacrolimus/MMF based immunosuppression (IS) was weaned and discontinued at one year if durable chimerism and normal kidney function and transplant biopsy were confirmed.

Results: Durable chimerism enabled complete withdrawal of IS in 26/37 patients. Comparison of clinical outcomes in FCR001 and a SOC cohort showed comparable patient survival and graft survival at two, three and five years. Cardiovascular medication usage was more frequent in SOC than in tolerant FCR001 subjects for hypertension (83% vs 18%) and hyperlipidemia (43% vs 9%). Graft function (eGFR) was better and more stable for the FCR001 cohort compared to SOC, with the difference due to patients with durable chimerism and off IS. Urinary cell mRNA profiling of a subgroup of FCR001 patients identified a potential signature of tolerance, characterized by increased levels of CTLA4 mRNA, and a higher ratio of CTLA4 mRNA to mRNA for granzyme B and perforin mRNA. If validated, such a signature of tolerance might help identify kidney transplant patients in whom reduction of IS drugs might be safely undertaken. To date, we have accumulated approximately 235 patient-years of exposure to FCR001 in LDKT, and the safety profile is consistent with that expected if a patient were to receive both a kidney transplant and an allo-HSCT with nonmyeloblastic conditioning.

Conclusions: We continue to monitor the patients in the Phase 2 trial for long-term safety and durability of immune tolerance and graft function. We are currently enrolling patients in FREEDOM-1, a randomized, controlled, open-label Phase 3 trial in the US in adult LDKT recipients.

Funding: Commercial Support - Talaris Therapeutics.

Preserved Kidney Allograft Function and Unique Urinary Biomarker Profiles in Living Donor Kidney Transplant (LDKT) Patients Tolerated with an Investigational Allo-Hematopoietic Stem Cell Transplantation Therapy

Elevation of Serum IL-8 in Patients with Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy

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Background: Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several different hematopoietic malignancies and disorders. However, HSCT-associated thrombotic microangiopathy (TA-TMA) represents a major obstacle to the success of this procedure in transplant recipients, and rapid progression to end-stage renal disease is a major complication of this disorder, affecting nearly 1 in 3 patients. Here, we sought to identify a serum biomarker for the detection of TA-TMA and investigate its role in the pathogenesis of this severe disease.

Methods: We measured the concentrations of several different cytokines and vasoactive peptides in the sera of 14 adult human HSCT recipients at the time of transplantation and again at 5-6 weeks following HSCT. Levels of IL-1β, IL-6, IL-8, TNF-α, IFN-γ, VEGF-B, HIF1β, and IL-17 were measured, using the highly sensitive ELISA single molecule array (Simoa) method.

Results: Statistical analysis of the change in each of the cytokines revealed that IL-8 was the sole marker that increased significantly over time in the TMA group. Next, we found that co-culture of irradiated peripheral blood mononuclear cells (PBMCs) with human umbilical vein endothelial cells (HUECs) resulted in increased IL-8 expression by the PBMCs. Furthermore, in vitro treatment of HUECs with IL-8 increased platelet adhesion and vWF expression. Treatment of platelets independently with IL-8 also increased their adhesion in vitro to HUECs. Finally, treatment of HUECs with IL-8 also induced senescence, and platelets were found to adhere more readily to senescent HUECs in vitro. Moreover, exposure of these HUECs to a senolytic agent abrogated the platelet adhesion.

Conclusions: These findings implicate IL-8 as a potentially important thrombogenic and pathogenic factor in TA-TMA. In addition, these data highlight senescence of endothelial cells for the first time as a possible mechanism for the microvascular thromboses observed in TA-TMA patients, suggesting that modulation of IL-8 could be an effective therapeutic pathway for this severe disease.

Funding: NIDDK Support, Other NIH Support - NIAID.

Three Distinct Phases in the Amount of Total and Donor-Derived Cell-Free DNA Are Observed Over Time in Plasma from Kidney Transplant Recipients


Background: Donor-derived cell-free DNA (dd-cfDNA) is a clinically validated biomarker for allograft rejection in kidney transplant (KT) recipients. Fluctuations in the total amount of cfDNA (including donor and recipient-derived cfDNA) can impact the reported dd-cfDNA fraction. Here we analyzed the changes in total and dd-cfDNA quantity, over time, in KT patients.

Methods: We selected 3,925 samples from 747 clinically stable patients with >3 longitudinal samples. The median time from KT to sample collection was 134 days (range: 1 day - 37 years). Total cfDNA and dd-cfDNA were measured using the Prospera™ assay and expressed as relative units per ml plasma (RU/ml). Dynamic changes in dd-cfDNA and total cfDNA over time were compared to their respective medians for all samples at 3-year post-KT, defined as reference.

Funding: Commercial Support - Talaris Therapeutics.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: One week following KT, median quantities of total cfDNA were elevated ~2-fold compared to the reference value on the first month. At month 3, a 1.6-fold increase was observed, which normalized to the reference value over the first year post-KT. In contrast, the absolute quantity of dd-cfDNA was initially elevated ~100-fold above the reference (1.06 IU/ml post-KT), which normalized over the first year post-KT. Thus, while preservation induced an elevation in total cfDNA during the first week is likely due to trauma to the donor organ from surgery. Additionally, a significant elevation in both total and dd-cfDNA was observed in patients who received a kidney from a deceased donor as compared to a living donor.

Conclusions: Total and dd-cfDNA levels were highly dynamic in the first year post-KT but stabilized afterwards. Further investigation is needed to determine the causes of total-cfDNA increases at months 3 and 4. Potential factors include inflammatory responses and NETosis, viral infection or transient interstitial fibrosis and tubular atrophy (IF/TA) in the kidney. The time-dependent dynamics were statistically significant, and in the high coefficient of variance (CV>50%), which limits extrapolations to individual patients. Potential variability should be considered when interpreting dd-cfDNA tests performed within the first week post-KT.

PO2044
A Peripheral Blood Transcriptomic Signature Predicts the Progression of Chronic Kidney Damage Post Transplant
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Background: Chronic kidney damage post-transplant is a major risk of allograft loss. The aim of this study was to identify a transcriptomic signature from peripheral blood collected at 3 months post-transplant to predict the progression of chronic kidney damage after transplantation.

Methods: We inspected kidney functional and histologic changes from the baseline (pre-implantation) to 1 year post-transplant in 112 kidney transplant recipients from the prospective Genomics of Chronic Allograft Rejection (GoCAR) study and identified the patients who developed chronic kidney damage within 1 year (progressors). We then carried out whole blood RNA-seq on the whole blood collected from these patients at 3 months post-transplant to identify a transcriptomic signature predictive of the progression of chronic kidney damage in the training set and validated by the testing set.

Results: Among 112 patients, we identified 30 progressors who developed kidney damage within 1 year post-transplant with a Chronic Allograft Damage Index (CADI) score increase by a 2, and 55 non-progressors with a normal histology at the baseline (CADI<2) and 12 months (CADI<2) post-transplant. The remaining 27 patients had a histological lesion at the baseline with a high CADI >2 but no progression at 12 months. From the progressors and non-progressors (total n=85), we randomly selected 55 patients as a training set and the remaining 30 patients as a testing set. From the training set, we identified a 9-gene set that predicts kidney damage at 12 months with AUC=0.88 and validated the prediction model in the testing set with AUC=0.79, superior to the Kidney Donor Risk Index (KDRI) in the deceased-donor population. The 9-gene set performed moderately in the patients who received a kidney with an intermediate or severe pathological lesion (n=27, AUC=0.68).

Conclusions: We presented a useful blood transcriptomic signature to accurately risk-stratify patients with chronic kidney damage post-transplant, especially for those patients who received a healthy kidney.

Funding: Other NIH Support - NIAID

PO2045
Kidney Precooling Improves Renal Outcome After Transplantation due to Preserved Mitochondrial Function
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Background: Transplanted organs experience several episodes of ischemia and ischemia-reperfusion. Ischemia-reperfusion injury (IRI) has remained one of the most serious hurdles for the survival of transplanted grafts. Temperature plays an important role in cellular metabolic rates since biochemical reactions are highly temperature dependent. Therefore, ischemia-triggered degenerative reactions could be mitigated by lowering tissue temperature. Whether a local hypothermia on kidney before blockage of blood flow protects kidney grafts against IRI has not been investigated.

Methods: In the present study we performed kidney transplantation and applied local hypothermia on the donor kidney before blockage of renal blood flow, which procedure is called “kidney precooling”. Kidney injury and function were evaluated at 7 days after transplantation.

Results: kidney precooling improved graft functions by >47% compared with abnormal control kidneys. The TA tissue proteome exhibited changes of kidney precooling associated with preserved mitochondria function and significantly delayed ATP depletion. More impressively, the precooling enables us to double the storage time of the donor kidneys in preservation solution in rats. Retrospective analysis of patient data also showed clear association between kidney precooling and kidney graft function.

Conclusions: Taken together, reduction of the cellular metabolism and enzymatic activity to a minimum level before ischemia protects kidney graft against IRI during transplantation.

Funding: NIDDK Support

PO2046
p53 Is Activated in Cold Storage/Transplantation to Mediate Tubular Injury and Renal Graft Dysfunction
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Background: Kidney injury associated with cold storage/transplantation is a leading cause of delayed graft function and poor outcome of renal transplants. p53 has been implicated in both ischemic and nephrotoxic kidney injury, but its involvement in kidney cold storage/transplantation is not clear. This study aimed to investigate the role of p53 in cold storage/transplantation kidney injury and test the therapeutic effects of p53 inhibitors.

Methods: Donor kidneys from C57BL/6 mice were preserved in ice-cold University of Wisconsin (UW) solution for 0.5, 2, 6 or 8.5h and transplanted into syngeneic recipients for 24h. Tubular injury, cell death and p53 activation were observed and their correlations were assessed. The acute response of kidneys from pifithrin-α and DMSO (the vehicle solution) treated mice was examined and compared, as well as response of kidneys from p53 conditional knock out (KO) mice and their wild type (WT) littermates.

To explore the therapeutic potential of p53 inhibition, pifithrin-α was also administered to test its effect on graft injury and function on day 6, when the graft became the sole life-supporting kidney after native kidney removal at day 5. Rat kidney proximal tubule cells (RPTCs) were incubated in UW solution at 4°C for cold storage, followed by full medium replacement at 37°C for rewarming. Pifithrin-α was added to UW solution or dominant negative p53 was transfected into RPTCs, for the purpose of evaluating their effect on RPTCs death in cold storage/rewarming.

Results: p53 was activated in kidney tubule cells during cold storage transplantation, which correlated with tubular injury and cell death. Pifithrin-α significantly reduced acute tubular injury, cell death and inflammation during cold storage/transplantation. Similar effects were shown by ablation of p53 specifically from kidney proximal tubule cells as well as pifithrin-α and dominant negative p53. Therefore, pifithrin-α and dominant-negative p53 could attenuate RPTC cell death during cold storage/rewarming.

Conclusions: p53 plays a critical role in kidney injury and dysfunction during cold storage/transplantation. p53 inhibitors may provide therapeutic benefits for donor kidney preservation and transplantation.

Funding: NIDDK Support, Veterans Affairs Support

PO2047
Multi-Omics Analysis Reveals Regulatory Mechanisms in Chronic Cyclosporine A-Induced Nephrotoxicity Studied in a Rat Model
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Background: Chronic calcineurin inhibitor (CNI) nephrotoxicity is a major drawback in current immunosuppressive regimens. In the chronic setting, arteriolar hyalinosis, decreased glomerular filtration rate, interstitial fibrosis and tubular dedifferentiation are the major adverse side effects. Regimens with cyclosporine A (CsA) and tacrolimus (Tac) have been compared before the background of potentially more harmful effects of CsA. Conversely, CsA is still widely used in transplant recipients and has been considered for replacement of Tac in posttransplant diabetes. To identify regulatory mechanisms in CNI nephrotoxicity we used quantitative transcriptomic, proteomic and phosphoproteomic methods. We tested the hypothesis that tubulointerstitial pathomechanisms play a significant role in chronic CNI nephropathy.

Methods: Whole transcriptome RNA-seq as well as global proteomic and phosphoproteomic methodologies were performed on kidney extracts from normal Wistar rats receiving CsA (25mg/kg b.w./day) or vehicle for 3 weeks. Differentially expressed genes and proteins as well as their phosphorylation status were obtained.

KEGG pathway and GO analysis from proteomics largely corresponded to the RNA-seq data. We identified 342 transcripts upregulated which included Ribosome genes and proteins as well as their phosphorylation status were obtained.

Conclusions: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Calcineurin Inhibitor Nephrotoxicity as Viewed by Comparative Analysis of the Effects of Cyclosporine A vs. Tacrolimus on Epithelial Pathology in Rodent Models


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Background: Calcineurin inhibitors (CNI) are widely used in immunosuppression in transplant recipients. Although essentially beneficial, their nephrotoxicity may cause or aggravate renal disease. We have challenged the hypothesis that the safety of the commonly applied CNI, cyclosporine A (CsA), and tacrolimus (Tac), differs regarding tubulointerstitial pathology. Mechanisms of proteinosis, autophagy and lysosomal dysfunction are addressed.

Methods: We have compared the effects of CsA and Tac in rat and mouse models. A focus was set on epithelial alterations. Adult Wistar rats received CsA (25 mg/kg/d), Tac (2 to 6 mg/kg/d), or vehicle subcutaneously implanted minipumps. A megaminicient-deficient mouse model was tested for the role of endocytosis. After 4 wk kidneys were prepared for histopathology or biochemical analysis.

Results: In rats, CsA and Tac produced similar alterations in the tubulointerstitium (Fig. 1). Preferentially the initial proximal tubule (S1, and S2 segments) was affected, displaying dysmorphic lysosomes with peripheral LAMP1 signal, autophagic and mitophagic vacuoles. Dedifferentiation was focally strong, with loss of brush border, basement membrane thickening, and interstitial collagen accumulation. Alterations in unfolded protein response (UPR) and autophagy parameters included significant increases in p-eIF2a, pPERK, CHOP, BIP, and LC3B, and ATG5 products and enhanced epithelial TUNEL signal. Endocytosis was substantially impaired. Cultured NRK cells indicated sensitivity to chemical chaperones ameliorating proteinosis and revealed similar apoptosis rates upon CsA and Tac.

Conclusions: These results suggest that alterations in tubular epithelial proteinosis upon long term CsA- or Tac-induced nephrotoxicity are similar. Addressing restitution of epithelial proteinosis may have renoprotective potential for both drugs.

Cyclosporine A but Not Tacrolimus Promotes Pro-Apoptotic Endoplasmic Reticulum Stress in Cultured Kidney Cells


Background: Current immunosuppressive regimen in organ transplantation include calcineurin inhibitors (CNI), cyclosporine A (CsA) or tacrolimus (Tac), as the first-line therapy. Both CNI may produce renal side effects, which are typically stronger in patients receiving CsA. Sustained clinical demand for CsA requires improved understanding of mechanisms underlying its nephrotoxicity. CsA builds complexes with cyclophilins, whereas Tac recruits FKBP12 for calcineurin inhibition. We hypothesized that cytotoxic effects of CsA may be related with impaired chaperone function of cyclophilins resulting in endoplasmic reticulum (ER)-stress and pro-apoptotic unfolded protein response (UPR).

Methods: Effects of CsA vs. Tac (10 µM for 6 h) on the UPR signaling were compared in cultured native HEK293 cells, as well as in genetically modified cells lacking critical ER-stress sensors, PERK or ATF6. An established ER-stress inducer, thapsigargin (Tg) served as a positive control.

Results: CsA and Tg, but not Tac, induced ER-stress and UPR in native HEK293 cells, which was reflected by increased abundance of key UPR products (CHOP, spliced XBP1, and phosphorylated IRE1α). Furthermore, CsA but not Tac increased spliced XBP1, and phosphorylated IRE1α. Furthermore, the CsA-dependent ER-stress was significantly reduced by concomitant application of chemical chaperones, TUDCA or 4-PBA.

Conclusions: In summary, these results suggest that renal side effects of CsA are partially mediated by suppression of cyclophilins, ER-stress, and pro-apoptotic UPR. Pharmacological modulation of UPR bears potential to alleviate the CsA nephrotoxicity.

Funding: Government Support - Non-U.S.
PO2052
Increased Autoantibodies Against Ro/SS-A, CENP-B, and La/SS-B in Patients with Kidney Allograft Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) causes >50% of late kidney graft losses. In addition to anti-HLA donor-specific antibodies (DSAs), antibodies against non-HLA antigens are also linked to AMR. Identifying key non-HLA antibodies will improve outcomes and guidance of AMR.

Methods: We analyzed non-HLA antibodies in sera from 80 kidney transplant patients with AMR, mixed rejection, acute cellular rejection (ACR), or acute tubular necrosis (ATN). IgM and IgG antibodies against 134 non-HLA antigens were measured in serum samples collected pre-transplant or at the time of diagnosis.

Results: Fifteen non-HLA antibodies were significantly increased (p<0.05) in AMR and mixed rejection compared to ACR or ATN pre-transplant, and seven at diagnosis. AMR and mixed cases showed significantly increased pre-transplant levels of IgG anti-Ro/SS-A and anti-CENP-B, compared to ACR. Together with IgM anti-CENP-B and anti-La/SS-B, these antibodies were significantly increased in AMR/mixed rejection at diagnosis. Increased IgG anti-Ro/SS-A, IgG anti-CENP-B and IgM anti-La/SS-B were associated with the presence of microvascular lesions and class-IIDSA (p<0.05). Significant increases in IgG anti-Ro/SS-A and IgM anti-CENP-B antibodies in AMR/mixed rejection compared to ACR were reproduced in an external cohort of 60 kidney transplant patients.

Conclusions: This is the first study implicating autoantibodies against Ro-SS-A and La/SS-B in AMR. These antibodies may participate in the crucial interplay between autoimmunity and alloimmunity in kidney AMR.

PO2053
A Sliding Window Approach to Investigate the Role of Donor-Recipient Intervindividual Genetic Distance on Kidney Transplant Outcome

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Background: Although the role of HLA matching on kidney transplant outcome is well appreciated, the role of genetic matching between donors and recipients outside of the HLA region is less well understood. This is important as histological damage is a major issue in allografts and studies have suggested that non-HLA immune factors play a significant role in this process. However, the mechanism involved is presently unknown.

Results: Unsupervised hierarchical clustering identified a subset of patients with increased pro-inflammatory cytokine levels (Figure a, cluster 2). This patient subset (N=20) was highlighted by high prevalence (75%) of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) (Figure b) and histological rejection (70%), and had worse graft survival compared to the group with low cytokine levels (N=172, HLA-DSA in 1.7% and rejection in 33.7%). Serum C-reactive protein and polymavirus and/or CMV viremia did not differ between the two clusters. Thirty percent of patients with high pro-inflammatory cytokine levels and HLA-DSA did not have histological rejection. Single-cell RNAseq analysis on public data from kidney transplant biopsy demonstrated expression of these cytokines in endothelial cells, non-classical monocytes and natural killer cells. We confirmed the inflammatory cytokine profiles in in vitro models of HLA-DSA-mediated crosstalk between endothelial cells, NK cells, and monocytes.

Conclusions: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.

PO2054
Prevention of Triglyceridemia by (Non-)Anticoagulant Heparin(oids)

Does Not Preclude Transplant Vasculopathy and Glomerulosclerosis

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Background: Chronic Transplant Dysfunction (CTD) is associated with increased PCSK9 and dyslipidemia. We recently showed defective lipoprotein clearance by increased PCSK9-hepatic syndecan-1 interaction in renal condition. Targeting PCSK9 by heparin(oids) might be a therapeutic option to improve dyslipidemia and CTD. We investigated the effects of (non-)anticoagulant heparin(oids) on serum lipids, syndecan-1 and PCSK9 levels and CTD development.

Methods: Kidney allotransplantation was performed from female Dark Agouti to male NZW donors. Fischer recipients received daily subcutaneous injections of saline, unfractonated heparin, RO-heparin or NAC-heparin (2mg heparin(oid)/kg BW) until sacrifice after 9 weeks of treatment.

Results: Saline-treated recipients developed hypertension, proteinuria, and loss of creatinine clearance, (all p<0.05 compared to baseline), along with glomerulosclerosis and arterial neointima formation. Heparin(oid)-treated recipients showed significant increase in plasma TGs (p<0.05), borderline increase in non-HDLc to HDLc ratio (p=0.051), approximately 10-fold increase in serum syndecan-1 (p<0.03), without significant increase in serum PCSK9 levels at 8 weeks compared to baseline. Heparin and non-anticoagulant RO-heparin administration in transplanted rats completely prevented increase in TGs compared to saline treated recipients at 8 weeks (both p<0.05). Heparin(oids) treatment did not influence serum TC, plasma syndecan-1 and PCSK9 levels, creatinine clearance, albuminuria, glomerulosclerosis and arterial neointima formation, 8 weeks after transplantation. Combining all groups, increased syndecan-1 shedding was associated with TC (r=0.5; p=0.03) and with glomerulosclerosis (r=0.53; p=0.021), whereas non-HDLc/HDLc ratio associated with neointima score in the transplanted kidneys (r=0.65; p=0.01).

Conclusions: Prevention of triglyceridemia by (non)anticoagulant heparin(oid) did neither influence PCSK9/syndecan-1, nor precluded CTD, which did however associated with shedding of lipoprotein clearance receptor syndecan-1 and unfavorable cholesterol profile.

PO2055
RBT-9 Antiviral Activity Against BK Virus

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Background: BK virus, a member of the polyomavirus family, is a significant risk factor for nephropathy and subsequent allograft loss in patients undergoing kidney transplantation. There are currently no approved treatments for BK virus-induced nephropathy. RBT-9, a novel formulation of stannous protoporphyrin (SnPP), exhibits broad antiviral activity against enveloped and nonenveloped viruses in vitro. It is also known to have protective effects against acute kidney injury (AKI) in animals when given prior to insult. Given the dual antiviral and kidney protective effects of RBT-9, the effect of RBT-9 against BK viral infection was investigated in vitro, as standard in vivo models that mimic BK viruria are not available.

Methods: Two conditions were investigated: 1) standard qPCR-based antiviral assay – treatment with RBT-9 at the time of infection and 2) viral neutralization – pre-incubation of RBT-9 with BK virus for 1 hour prior to infection. RBT-9 was tested at concentrations up to 100 μM. Human foreskin fibroblast (HFF) cells were used as the host cell. Viral activity was assessed by real time qPCR and cellular viability was determined by CellTiter-Glo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: RBT-9 exhibited moderate antiviral activity against BK virus under both treatment conditions. The 50% effective concentration (EC$_{50}$) averaged 5.5 μM in 2 independently run standard qPCR assays and 5.4 μM in the neutralization assay. The EC$_{50}$ of RBT-9 in these assays is 11 times lower than the highest dose of RBT-9 tested in Phase 1 studies and considered to be well tolerated. The 50% cytotoxic concentration (CC$_{50}$) in the in vitro studies averaged 92.9 μM, indicating RBT-9 did not adversely affect host cell viability at concentrations 16.5 times higher than its effective concentration.

Conclusions: Given the antiviral activity of RBT-9 against BK virus in vitro and the safety profile of RBT-9 in Phase 1 human studies, a clinical study assessing the efficacy of RBT-9 is warranted in patients who are at risk of developing BK virus-induced nephropathy.

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PO2056

The Survival Benefit of Re-Kidney Transplantation in Older and Younger Patients with Graft Failure

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Background: The survival benefit of re-kidney transplantation (re-KT) has been demonstrated two decades ago in younger patients. The proportion of patients with graft failure is increasing, particularly among those aged 65+. We compared the survival benefit of re-KT by patient age.

Methods: Using data from the Scientific Registry of Transplant Recipients, we identified 42,366 patients who experienced graft failure after their first KT and were listed for re-KT between 1990-2019. We treated re-KT as a time-dependent variable and used Cox regression to compare the risk of mortality between being listed for a re-KT and undergoing re-KT. We used the inverse probability weighting method to account for potential confounding. We also tested whether the risk of mortality differed by patient age at listing (18-64 vs 65+ years) using a Wald test.

Results: Overall, 42,366 patients were listed for re-KT and 47.5% underwent re-KT by 10/31/2020. The number of patients being listed for re-KT tripled between 1990 and 2019. The mortality rate was 6.6 per 100 person-years among patients being listed and 3.0 per 100 person-years among those re-transplanted. Overall, the risk of mortality was lower after re-KT than during listing (adjusted hazard ratio [aHR]=0.64). However, the association differed by age (P interaction =0.03), but the survival benefit of retransplantation was observed among both younger (aHR=0.42) and older patients (aHR=0.49). The proportion of patients with graft failure was 5.5% in patients aged ≤65 years, and 9.5% in patients aged ≥65 years. The survival benefit of retransplantation was greater in younger patients with graft failure (aHR=0.42) than during listing (adjusted hazard ratio [aHR]=0.43). However, the survival benefit of retransplantation was only significant in younger patients (P=0.03).

Conclusions: Our finding suggests that re-KT is associated with a significant survival benefit in younger and older patients. In addition, long-term outcomes in older re-KT recipients were comparable to those in older first KT recipients. Transplant centers should consider expanding re-KT to appropriate older adults.

Funding: NIDDK Support, Other NIH Support - NIAID, NIA

Figure 1. Trends in being listed for retransplant and mortality rate per 100 person-years by calendar year of listing.

PO2057

Development and Determinants of Quality of Life After Kidney Transplantation in Elderly Recipients


Background: Kidney transplantation is regarded as the best treatment for end-stage kidney disease, with survival benefits also in elderly patients. However, little is known regarding (determinants of) health-related quality of life (HRQoL), and changes in HRQoL in elderly kidney transplant recipients (KTR).

Methods: We used data from KTR ≥65 years old at the time of kidney transplantation, enrolled in the ongoing prospective TransplantLines Biobank and Cohort Study. Data on HRQoL were assessed using SF-36 mental and physical component scores (MCS and PCS). Side effects of immunosuppressive drugs were assessed using MTSOSD-59R questionnaires. In a subgroup with available data on HRQoL before transplantation, we investigated HRQoL trajectories.

Results: We included 111 KTR (age 70±4 years, 39% pre-emptive and 45% living donors). At one year after transplantation, eGFR was 48±16 ml/min/1.73m, MCS was 51±8, and PCS was 52±7. MCS was lower in females (P=0.018), and in KTR that suffered from rejection in the first year (P=0.005). PCS was higher in KTR that were pre-emptively transplanted (P=0.010) and lower in those with post-transplantation diabetes mellitus (PTDM, P=0.008). Number of side-effects of immunosuppressive drugs was strongly associated with both MCS and PCS (both P<0.001). Age, eGFR, hemoglobin, post-transplant comorbidities, hospitalizations and infections in the first year were not associated with HRQoL. In 43 KTR with available data both before and after transplantation, PCS increased significantly after transplantation (48±52; P point year =0.001, Figure 1), while MCS did not significantly improve (49±51; P point year =0.095).

Conclusions: Medication-related side-effects, transplant rejection, transplantation after start of dialysis and PTDM were associated with worse HRQoL among elderly KTR, whereas eGFR and age were not. Moreover, HRQoL improves after kidney transplantation in KTR ≥65 years old.

Funding: None

PO2058

Elderly Kidney Transplantation Donors After Circulatory Death: Is It Worth It?

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Background: Kidney transplantation (KT) remains the treatment of choice for end-stage renal disease, since it offers better outcomes and quality of life and is less costly in the long run compared with stay on dialysis. In order to expand the donor pool, donation after circulatory death (DCD) has become an increasingly popular strategy, and eligibility criteria for this procedure have widened in the last few years.

Methods: Single-center retrospective study in which we described the clinical characteristics and outcomes of all the patients who underwent Maastricht category-III controlled DCD (cDCD) KT from January 2006 to October 2019. IBM SPSS (v25.0) was used for all the statistical analysis. Two-sided p values of <0.05 were considered statistically significant.

Results: We performed 54 cDCD KT, median follow-up was 36 (0.5-155) months. Donors’ mean age was 50.2 years (range 19-81), 20.4% were ≥70 years, 64.8% male, 22.2% diabetics, 25.9% suffered hypertension. 24 (44.4%) recipients presented delayed graft function and 6 (11.1%) suffered primary nonfunction, with no differences depending on donor age (a or <70 years). Primary nonfunction was the main cause of graft loss, which occurred in 8 patients (14.8%) and it was significantly higher in donors ≥70 years old (p=0.021). In the multivariable analysis only donor age ≥70 years was related to graft loss. Other factors examined such as cold ischemia time >14 hours, warm ischemia time >17 minutes and the presence of cardiovascular disease, didn’t show statistically significant differences. At one-year follow-up, renal function was significantly better in donors <70 years compared to donors ≥70 years, with mean serum creatinine 1.4 vs 2.1 mg/dl respectively (p=0.003), and estimated filtration rate 36.4 ± 19.79 vs 18.9 ± 11.73 ml/min per 1.73 m² (p=0.008). The mortality rate was higher among recipients from older donors (3 [23.7%] vs 2 [4.6%], p=0.021).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

630
PO2059

Immunosuppression, Osteoporosis, and Fractures in Younger and Older Adults After Kidney Transplantation

Krista L. Lentine,¹ Sarat C. Kuppuçi,² Ruixin Li,¹ Yasar Caliskan,³ Visit Cheungpasitporn,² Mark Schnitzer,⁴ Mara McAdams-DeMarco,⁳ Vikas R. Dharnidharka,⁴ YJoon B. Ahn,⁵ Sunjae Bae,⁶ Dorry L. Segev,⁷ Gregory Hess,⁸ Suphatani Bunnapradist,³ Henry B. Randall,⁷ David Axelrod,⁷ Saint Louis University School of Medicine, Saint Louis, MO; ²Mayo Clinic Rochester, Rochester, MN; ³Johns Hopkins University, Baltimore, MD; ⁴Washington University in St. Louis, St Louis, MO; ⁵Drexel University, Philadelphia, PA; ⁶The University of Iowa Hospitals and Clinics Department of Pathology, Iowa City, IA; ⁷University of California Los Angeles, Los Angeles, CA.

Background: Osteoporosis and fractures are important complications among kidney transplant recipients (KTx) that may be exacerbated by immunosuppression (ISx) and aging. We examined relationships of osteoporosis and fractures with ISx among older and younger adults in a national sample of Medicare beneficiaries.

Methods: We examined USRDS data (2005-2017) to explore associations of ISx regimens (within 6 mo) with osteoporosis and fracture diagnoses >6 mo-to-3 yr post-KTx among Medicare-insured younger (age <55) and older (aged ≥ 55) adults. We used multivariable Cox regression with inverse propensity weighting to compare cancer risk vs. reference regimen of Thymoglobulin (TMG) or Alemtuzumab (ALEM) + Tacrolimus + antimetabolite + prednisone.

Results: Among 67,362 KTx Medicare-insured recipients, the 3-year composite risk of osteoporosis and fractures varied by age and ISx regimen. Among older adults, incidence ranged from 11% with TMG/ALEM no Pred, to 16% in those managed with CsA and mTORI-based regimens (Fig. A) In adjusted models, TMG/ALEM + no Pred was y associated with lower risk (aHR, 0.84) than TMG/ALEM + triple therapy (Fig. B). Conversely, mTORI-based regimens (aHR, 1.23) and CsA-based regimens (aHR, 1.21) were associated with greater risk. Patterns were generally similar but relative impacts were amplified in younger patients, including greater benefits of steroid-avoidance (aHR, 0.55). Conclusions: Among Medicare insured KTx recipients, steroid avoidance after TMG/ALEM induction is associated with reduced risk of fractures and osteoporosis. Fracture risk is a consideration in tailoring ISx in older KTx recipients.

PO2060

Organ Procurement and Transplantation Network Effort to Increase Kidney Transplantation Through Kidney Accelerated Placement

Samantha Noren,¹ David Klassen,¹ Matthew Cooper,² Andrew Placona,¹ United Network for Organ Sharing, Richmond, VA; ²MedStar Health, Columbia, MD.

Background: In 2017 just over a quarter of kidneys deemed hard to place were transplanted while the rest were discarded. The Kidney Accelerated Placement (KAP) project aimed to increase the acceptance of these deceased donor kidneys, declined by a large proportion of programs, through the creation of a novel allocation system. Offering hard-to-place kidneys to transplant centers with a history of transplanting similar organs, utilization would increase by reducing time to find an acceptor and cold ischemic time (CIT) within the deceased organ allocation process. We hypothesized CIT mediated the effect of KAP on transplant center organ-level offer acceptance.

Methods: We used a pre/post design mediation analysis with OPTN database offers from kidney matches meeting criteria for KAP 7/18/18–7/15/19 (pre-KAP) and 7/18/19–7/15/20 (KAP). We employed logistic regression models of KAP and CIT on organ acceptance and a linear regression model of KAP on CIT, adjusting for additional risk factors (Fig 1).

Results: Transplant center organ-level offer acceptance rates were 0.37% (pre-KAP) and 0.23%(KAP). The total effect indicates that KAP increased odds of acceptance by 0.07. Decreases in CIT increased odds of acceptance by 0.02 (indirect effect) and the remaining portion of the total effect is attributable to other possible mechanisms (direct effect).

Conclusions: While KAP offered a higher rate of acceptance, the magnitude of the effect was small. Because the baseline level of offer acceptance was also small, our analysis indicates that KAP works conceptually to increase the use of these kidneys. At the same time, there is evidence that alternative approaches to KAP are needed to potentially decrease organ discard. Future iterations plan to consider complex risk adjustment including behaviors and the differential impact for donor types.
PO2062
Association of Medicaid Expansion with Medicaid Uptake and Uninsur-
ance Among US Kidney Transplant Recipients
Elizabeth Kotzep, Randal K. Detwiler, Jennifer E. Flythe. UNC Kidney Center; Chapel Hill, NC.

Background: The differential uptake of Medicaid expansion among U.S. states following the Affordable Care Act created a natural experiment to investigate the association between Medicaid expansion and health insurance usage patterns among kidney transplant (KT) recipients. Adolescents and young adults (AYA) are at particular risk for insurance access disruption.

Methods: Using data from the Scientific Registry of Transplant Recipients, we constructed a multivariable difference-in-differences model to evaluate the association between living in a state with Medicaid expansion (vs. a state without) and two outcomes: primary insurance of Medicaid at the time of KT, and being uninsured 5 years following KT. We included U.S. recipients of kidney-alone transplantation between 1/1/2005 and 3/12/2020. We analyzed AYA (ages 15-26 years) and other nonelderly adults (ages 27-64 years) separately.

Results: The AYA group included 17,158 KT recipients, while the group of adults 27-64 years included 198,914 KT recipients. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on use of Medicaid as the primary insurance type at the time of KT was +1.9% (95% CI -0.4% to +4.3%) for the AYA group and +1.7% (95% CI +1.3% to +3.1%) for the non-AYA group. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on being uninsured 5 years after KT was +3.6% (95% CI +2.0% to +5.1%) for non-AYAs and +1.2% (95% CI -0.7% to +3.1%) for AYAs.

Conclusions: Living in a Medicaid expansion state was associated with greater use of Medicaid at the time of KT for adults ages 27-64, but not in the AYA group. In both age groups, living in a Medicaid expansion state was associated with a modest reduction in being uninsured 5 years following KT. Increased access to Medicaid may provide a protective effect against becoming uninsured after KT.

Funding: NIDDK Support

Results of difference-in-differences analyses examining the association between Medicaid expansion and insurance outcomes among U.S. KT recipients.*

*Adjusted for gender, race/ethnicity, cause of kidney failure, year of KT, and state fixed effects.

PO2063
Construct Validity of the Patient-Reported Outcomes Measurement Information System (PROMIS®) Profile Summary Scores in Patients with Kidney Failure
Istvan Mucsi,1 Gauree Chawla,1 Anqi Chen,1 Mark JP M. Sanchez,1 Nathaniel Edwards,1 John D. Peipert,2 Madeline Li,3 Doris Howell,3 Susan J. Bartlett,4 Ron D. Hays.5 Kidney Health Education and Research Group 1University Health Network, Toronto, ON, Canada; 2Northwestern University Feinberg School of Medicine, Chicago, IL; 3Princess Margaret Hospital Cancer Centre, Toronto, ON, Canada; 4McGill University, Montreal, QC, Canada; 5University of California Los Angeles, Los Angeles, CA.

Background: The PROMIS® profiles include a singular pain intensity item and 7 multi-item scales (e.g., physical function, fatigue, depression, social participation, etc.). These domains can be summarized into physical (PHS) and mental health summary (MHS) scores. We examine correlations of the PHS and MHS with the SF-12 physical (PCS) and mental component score (MCS), the Patient Health Questionnaire (PHQ-9), EQ-5D-5L, KDQOL-36 symptom scores, and serum albumin. The PHS was hypothesized to be strongly associated with other measures of physical health, and the MHS with other measures of mental health.

Methods: Cross-sectional convenience sample of 606 adults. Higher PHS and MHS scores correspond to better health. We estimated correlations of the PHS and MHS with the SF-12 physical (PCS) and mental component score (MCS), the Patient Health Questionnaire (PHQ-9), EQ-5D-5L, KDQOL-36 symptom scores, and serum albumin. The PHS was hypothesized to be strongly associated with other measures of physical health, and the MHS with other measures of mental health.

Results: Correlations with the PROMIS PHS and MHS (Table) with legacy health-related quality of life measures were large. The patterns of correlations of the PHS and MHS were consistent with a-priori hypotheses. Patients on dialysis were older (mean[SD] age 64(14) vs 50(15) years), and less likely to be White (32% vs 68%); p<0.01 for all. Kidney transplant recipients reported better health than patients on dialysis: PHS (mean[SD] 47[10] vs 37[9], p<0.001) and MHS (50[9] vs 45[9], p<0.001) and this remained significant in multivariable adjusted (age, sex, ethnicity, marital status, comorbidity, serum albumin and hemoglobin) regression models (coefficient[95% CI] of difference between dialysis and transplant for PH-SF 5.2 [1.6-7.7]; for MH: 3.2 [1.0-5.3]; both p<0.01).

Conclusions: These results support the construct validity of PROMIS PHS and MHS scores among patients treated with kidney replacement therapies. PHS and MHS was substantially better among kidney recipients compared to patients on dialysis.

Table

<table>
<thead>
<tr>
<th>Measure</th>
<th>PHS</th>
<th>MHS</th>
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<tbody>
<tr>
<td>SF-12 PCS</td>
<td>0.74</td>
<td>0.72</td>
</tr>
<tr>
<td>SF-12 MCS</td>
<td>0.57</td>
<td>0.56</td>
</tr>
<tr>
<td>PHQ-9</td>
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</tr>
<tr>
<td>EQ-5D</td>
<td>0.68</td>
<td>0.70</td>
</tr>
<tr>
<td>KDQOL-36</td>
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<td>0.78</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.53</td>
<td>0.52</td>
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</tbody>
</table>

Footnote: * Adjusted for gender, age, race/ethnicity, cause of kidney failure, year of KT, and state fixed effects.

PO2064
Association of Physical Performance with Death or Delisting in Patients Waitlisted for Kidney Transplantation
Anoop Sheshadri,1,2 Elaine Kau,1 Deborah B. Adey,2 Jennifer C. Lai,2 Kirsten L. Johansen.3 San Francisco VA Health Care System, San Francisco, CA; 2University of California San Francisco, San Francisco, CA; 3Hennepin Healthcare, Minneapolis, MN.

Background: Patients awaiting kidney transplantation (KT) often report impairments in functional status, which are associated with higher risk of death or delisting. However, self-reported functional status is subjective and can differ from objective assessments of physical performance. We sought to determine whether objective metrics of physical performance were associated with death or delisting prior to KT and whether these metrics improve prediction of death or delisting compared with more routinely available clinical data.

Methods: We enrolled 443 patients from the UCSF KT clinic from 12/17-3/20 at an initial or re-evaluation for eligibility for a first KT. We administered the Short Physical Performance Battery (SPPB; including gait speed, balance, and sit-to-stand) and measured grip strength by dynamometer. We performed univariable and multivariable Cox models to examine the association between physical performance and death or delisting. We created models using combinations of metrics in addition to a “base” model for death or delisting (age, sex, diabetes, CAD, CVD, PVD, years on dialysis) and calculated Harrell’s concordance index for each model.

Results: Median age was 55 years, and 63% were male. Median SPPB score was 10 (8, 11), with 25.1% having gait speed <0.8 m/s. In multivariable analysis, lower SPPB and slower gait were associated with higher risk of death or delisting, and higher grip strength with lower risk (Table 1). Compared with the base model (C-index 0.70, strongest predictor: age), addition of SPPB (0.74, p=0.03) and SPPB + grip strength (0.75, p=0.03) improved discrimination.

Conclusions: SPPB, grip strength, and slower gait were associated with death or delisting. SPPB and grip strength improved prediction of death or delisting. Transplant centers should consider routinely evaluating physical performance for waitlisted patients to help with clinical decision making.

Funding: NIDDK Support

Association of physical performance with death or delisting among 443 patients evaluated for primary KT

<table>
<thead>
<tr>
<th>Measure</th>
<th>SPPB</th>
<th>Grip strength (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>2.26 (1.70, 3.02)</td>
<td>1.99 (1.4, 2.81)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;4</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>2.95 (2.24, 3.87)</td>
<td>1.99 (1.4, 2.65)</td>
</tr>
<tr>
<td>p-value ***</td>
<td>&lt;4</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

**SPPB: 10-12 [ref], 7-9, 4-6, <4
**Linear test for trend among categories of SPPB p <0.01
***Adjusted for covariates in “base” model

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

632
PO2065
Development of a Conceptual Model to Understand Disease Burden in Kidney Transplantation
Chris Marshall,1 Garima Sharma,2 Christel Naujoks,3 Hakam Gharbi,2 Hannah C. Pegram,1 Natalie V. Althouse,1 Fiona Brown,1 Daniel Kuessner.2
1DRG Abacus (Part of Clarivate), London, United Kingdom; 2Novartis AG, Basel, Switzerland.

Background: While kidney transplantation offers patients with end stage kidney disease significant health benefits compared to dialysis, the immunosuppressive therapies designed to improve graft survival result in complex treatment regimens and side effects for patients. The development of new therapies to reduce this patient burden and improve long-term patient outcomes is needed. To guide selection of patient-reported outcome (PRO) measures for clinical trials, it is important to understand how patients feel or function related to a health condition or its treatment. This study sought to develop a preliminary conceptual model in kidney transplantation to provide a visual representation of the concepts of importance to patients (signs, symptoms, and impacts).

Methods: A targeted review of published literature was conducted in Embase, Medline, and PsycInfo databases to identify qualitative articles describing the patient experience following kidney transplantation and associated use of immunosuppressive treatment. Studies were selected based on number of concepts and direct patient quotations available for thematic analysis.

Results: From 61 eligible publications identified for full-text review, 20 were selected for data extraction. All studies involved qualitative interviews, focus groups, or analysis with kidney transplant recipients, and were conducted across various geographic locations (US, Europe and Australia). The most frequently reported concepts across studies included: ‘feeling anxious/worried’ (100%, n=20); ‘feeling distressed, overwhelmed’ (75%, n=15); ‘fatigue’ (60%, n=12); and ‘weight gain/loss’ (60%, n=12). The conceptual model identified nine domains to group the concepts as reported in the literature. These domains were delineated into the proximal effects of kidney transplantation (side effects and illnesses; physical/cosmetic changes; functional limitations; taxing medication regimen; and frequent medical appointments); and the more distal impacts (impacts on emotions, work, lifestyle, and relationships).

Conclusions: The conceptual model was based on a rich source of patient quotes and provides an important first step to understand the patient experience of kidney transplantation and inform the selection of PRO measures for use in clinical trials based on their conceptual coverage.

Funding: Commercial Support - Novartis

PO2066
Customizing PROMIS-Depression Computer Adaptive Testing Stopping Rules for Patients with Kidney Failure

Background: The Patient Reported Outcomes Measurement Information System Depression (PROMIS-D) computer adaptive testing (CAT) allows precise and tailored assessment of depressive symptoms. Due to the default stopping rules, many respondents without depression may need to answer 10-12 items. The maximum number of items required by the stopping rule can be reduced which could improve efficiency when the tool is used for screening. We assess the screening performance of customized CAT stopping rules in patients with kidney failure.

Methods: A cross-sectional convenience sample of adults with kidney failure treated with dialysis or kidney transplant completed PROMIS-D CAT as well as the Patient-Health Questionnaire-9 (PHQ-9). Moderate/severe depressive symptoms were defined as a PHQ-9 cut-off score ≥10. Sociodemographic and clinical characteristics were obtained from self-report and medical records. All patients completed CAT using the original stopping rule (CAT), that requires a reliability of ≥0.90 or maximum 12 items. We compare this to three simulated CAT configurations with maximum 8, 6 and 4 items (CAT, CAT, and CAT, respectively). Reliable T score range (reliability is ≥0.90), sensitivity and specificity of each version were assessed.

Results: Of the 336 patients, the mean SD age was 55(16), 63% were male, 49% were Caucasian and 32% were on dialysis. Based on PHQ-9, 16% reported moderate/severe depressive symptoms. Using a PHQ-9a10 as a reference for moderate/severe depressive symptoms, sensitivity and specificity of a T score of 55 with CAT was 79% and 81% respectively. CAT presented no change in the reliable range (T-score 41 to 84), while CAT, and CAT presented a small reduction in the reliable range (41-76 and 41-77 respectively) compared to CAT. Sensitivity and specificity of the modified CAT versions remained essentially the same.

Conclusions: Customizing PROMIS-D CAT stopping rules have the potential to improve efficiency of screening for moderate/severe depressive symptoms. This reduces questioning burden without change in the discrimination of the T score. A PROMIS-D CAT with modified stopping rule (maximum 6 or even 4 items) could be used for screening for depressive symptoms among patients with kidney failure.

PO2067
Pre-Transplant Sarcopenia Does Not Predict Graft Function or Mortality in Kidney Transplantation
Taylor Norris, Neal Montgomery, Shelby Fishback, Diane M. Cibrik, Aditi Gupta. University of Kansas Medical Center; Kansas City, KS.

Background: Sarcopenia is common in end stage kidney disease (ESKD), and is associated with increased risk of cardiovascular events and mortality. The association between pre-transplant sarcopenia and post-transplant outcomes is unknown.

Methods: We conducted a single-center retrospective study to evaluate the association between pre-transplant psoas muscle cross-sectional area at level of L4 and post-transplant outcomes; change in graft function, length of hospitalization, rehospitalization at 30- and 90-days post-transplant, graft loss, and mortality.

Results: Of the 573 patients with pre-transplant CT images, 465 received kidney transplant (KT) alone, 71 received simultaneous liver-kidney transplantation (SLK), and 37 received simultaneous pancreas-kidney (SPK) transplantation. Pre-transplant psoas muscle cross sectional area was associated with longer hospitalization in KT alone and SPK transplants, but not with post-transplant graft function, rehospitalization rates or mortality (Table 1).

Conclusions: Unlike ESKD patients on dialysis, pre-transplant psoas muscle cross-sectional area is not associated with adverse post-transplant outcomes. Thus, sarcopenia should not be an exclusion criterion for transplant eligibility.

Cox proportional hazard models (adjusted for age, sex, race and diabetes) for normalized psoas cross sectional area and post-transplant outcomes.

PO2068
Utility of Genetic Testing in Kidney Transplant Evaluation
Lauren Beretich,1 Neeraj Singh,2,3 Arianna Palermi,4 Aleza Qamar,2,3 Daniel Lukisc,1 Sarah McCormick,1 Hossein Tabriziani,1 Paul R. Billings.1
1Natera, Inc., San Carlos, CA; 2John C. McDonald Regional Transplant Center, Shreveport, LA; 3Wills-Knighton Physicians Network, Shreveport, LA; 4Arkansas College of Osteopathic Medicine, Fort Smith, AR.

Background: Genetic testing is an emerging tool in pre-kidney transplant (KT) evaluations for individuals with end-stage renal disease (ESRD). A known genetic etiology can inform the risk of disease recurrence, guide transplant management, and enable evaluation of living related donors. Despite these benefits, there is a paucity of literature describing the use of diagnostic genetic testing as part of the pre KT evaluation. Here we describe the initial experience incorporating a broad renal genetic testing panel for KT candidates in one Louisiana center.

Methods: A retrospective review was conducted on 31 patients that underwent a KT evaluation in April 2021 with Renasight®10, a NGS-based >380-gene kidney disease test. The patients were primarily female (20/31), African American (16/31), and <50 years of age (17/31). The primary clinical causes of CKD were hypertension (HTN) and/or diabetes (20/31).

Results: Positive findings were identified in 32.3% (10/31) of patients in the APOL1, CFI, COLA4A4, and PKD2 genes. Additionally, 29.0% (9/31) of the patients were identified as heterozygous carriers of autosomal recessive conditions. Of the positive cases, 60% (6/10) were either homozygous or compound heterozygous for the G1 and G2 risk alleles in the APOL1 gene. One individual, heterozygous for a likely pathogenic variant (c.577+10C>G) in the CFI gene, associated with atypical hemolytic uremic syndrome, along with biopsy-proven thrombotic microangiopathy was tested for complement proteins in plasma. Due to the potential increased risk of recurrence, simultaneous liver-kidney transplant and Eculizumab was considered.

Conclusions: In this initial experience, kidney genetic testing was an informative tool resulting in a change in patient management. The genetic testing yield in this cohort is likely enriched as many of these patients had a positive family history of kidney disease, significant proteinuria, or ESRD attributed to HTN. Genetic testing in pre-KT patients has potential clinical impact on post-KT management and selection of living-related donors. Further research is needed to describe the utility of genetic testing for kidney transplant candidates.
PO2069
Transplant Clinician Opinions on Use of Race in the Estimation of Glomerular Filtration Rate: A National US Survey Study
Krista L. Lentine,1 Neeraj Singh,2 Benjamin E. Hippen,2 Kenneth J. Woodside,3 Prince M. Anand,4 Matthew Cooper,4 Darshana M. Dadhania,4 Sruthi A. Ainiapurupu,5 Mona D. Doshi,1 1Saint Louis University School of Medicine, Saint Louis, MO; 2LSU Health New Orleans, New Orleans, LA; 3Geisinger Health, Danville, PA; 4Weill Cornell Medicine, New York, NY; 5University of Michigan Health System, Ann Arbor, MI; 6Metroliena Nephrology, Charlotte, NC; 7MedStar Health, Columbia, MD.

Background: Inclusion of race in eGFR calculation has raised controversies based on concern that assigning a higher GFR to Black patients delays opportunity for preemptive kidney transplant listing.

Methods: We conducted a survey of adult kidney transplant center staff in U.S. (12/17/2020–2/28/2021) to assess opinions on use of race-based estimated GFR (eGFR) equations for waitlisting and living donor candidate evaluation, availability of serum cystatin-C testing and measured GFR, and related practices.

Results: Respondents represented 57% (124/218) of adult kidney transplant centers and 76.3% of recent practice volume. Nearly 95% of respondents felt that current race-based eGFR calculators need revision, primarily due to concerns around healthcare disparities and inaccuracies around reporting of race, particularly among multi-racial individuals. A majority of respondents (70.5%) believed that elimination of race would allow preemptive kidney transplant wait listing for Black patients, but a similar number (69%) also raised concern that removing race from GFR estimation could incur harms. One-third of responding programs lacked or were unsure of availability of cystatin C or mGFR at their institution. Nearly 15% of responding centers have removed race from GFR estimation and were either reporting eGFR for non-Black or ranges; 46% were planning to do so and 39.5% did not plan to change for now (Figure). There was no difference in GFR acceptance threshold for Black versus non-Black living donors.

Conclusions: This national survey highlights a broad consensus that extant approaches to eGFR calculations are unsatisfactory, but a range of opinion on what should replace the status quo. National consensus, guidelines, and infrastructure for laboratory testing are necessary to facilitate best practices to prevent further disparities in transplant care.

PO2070
Defining the Living Donor Transplant Evaluation Process for Optimization of a One-Day Evaluation Program
Ariana Noel,1,2 Greg A. Knoll,1,2 Ann Bugeda,1,2 1University of Ottawa, Ottawa, ON, Canada; 2Ottawa Hospital, Ottawa, ON, Canada.

Background: Living donor transplantation provides patients with end stage kidney disease increased longevity and quality of life compared with dialysis. The donor evaluation process can be inefficient and costly for patients and the healthcare system. There is a paucity of research on evaluation optimization in living kidney transplantation. We investigated our living donor evaluation process to develop a one-day program, improving program efficiency.

Methods: Living donor staff and patient partner from The Ottawa Hospital Living Kidney Donor program participated in individual, semi-structured interviews to develop a Lucidchart process map of the donor evaluation process and ascertain the time associated with each step. A one-day evaluation program model was developed based on our process map and interview participant feedback. Amount of time for each step of the process was collected for future cost assessment.

Results: Mean time to complete the evaluation process and reach donor approval is 9 months. The donor evaluation process can be divided into 3 phases: Initial Interview, Phase I, and Phase II. Phase I requires the most nursing and administrative time. The greatest barriers to process efficiency are 24-hour urine collections to estimate kidney function and coordinator time spent on correspondence with laboratories. A one-day evaluation will reduce the evaluation process and approval to approximately 4 weeks. Greatest barriers for patients included need for increased education and time off work. Next steps will include cost estimates of the current program with the goal of implementing a one-day evaluation program at The Ottawa Hospital.

Conclusions: A one-day evaluation program will increase the efficiency of the living donor process for donors, coordinators, and recipients. Phase I investigations are a barrier to program efficiency and can be streamlined with a one-day evaluation. The development of donor educational resources will improve the donation experience for patients.

PO2071
Comparison of CT Volumetry vs. Nuclear Renography to Predict Remaining Kidney Function After Living Kidney Donation
Sang Hun Pum, Hanbi Lee, Chul Woo Yang, Byung Ha Chung, Seoul Saint Mary’s Hospital, Seocho-gu, Seoul, Republic of Korea.

Background: Computed tomography (CT) and nuclear renography are performed to decide kidney procurement. The aim of this study was to compare single kidney (sk) function and single kidney (sk) volume in predicting post-donation kidney function. Further, we aimed to investigate which modality is better to decide which kidney is more appropriate in terms of kidney function recovery, especially when the results were contradictory.

Methods: CT volumetry and nuclear renography from 835 kidney donors were retrospectively included. We investigated correlation between sk-volume and sk-mGFR and the agreement of two modalities. Mismatch was defined as sk-volume higher and sk-mGFR smaller than the other kidney, or vice versa. We compared the predictive value for post-donation kidney function between two modalities in total group and in mismatched group. Based upon decision preference, we compared kidney function recovery between two modalities at 6 months after donation.

Results: Mean baseline estimated GFR was 100.01 ml/min/1.73 m2. The mean right and left sk-volume were 171.18 and 179.71 cm3 and mean right and left sk-mGFR were 53.72 and 53.44 ml/min, respectively. 701 (83.96%) donated left kidney. Sk-mGFR and sk-volume showed significant correlation (r=0.484, P<0.001) and the results showed significant agreement in Bland-Altman plot and Intraclass correlation coefficient was 0.647 (P<0.001). In total group, CT volumetry was superior to nuclear renography in predicting kidney function after donation (1 month: β=0.402, P<0.001, β=0.242, P<0.001; 6 months: β=0.448, P<0.001, β=0.214, P<0.001) by multivariable linear regression analysis. In mismatched group (326 donors), CT volumetry still outweighed nuclear renography (1 month: β=0.453, P<0.001, β=0.259, P<0.001; 6 months: β=0.480, P<0.001, β=0.285, P<0.001). When mismatch occurred, 260 (79.75%) procurements were decided by nuclear renography. Functional recovery was higher in CT volumetry preferred group, although it did not reach statistical significance (33.99% vs 30.09%, P=0.098).

Conclusions: CT volumetry was appropriate to assess single kidney function and it outperformed nuclear renography in predicting kidney function after donation. Therefore, when contradictory results between left and right kidney occur, CT volumetry can be preferred in procurement strategy.
PO2072

The Impact of New-Onset Diabetes After Transplantation on Survival and Major Cardiovascular Events in Korean Kidney Transplantation Recipients

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Background: New-onset diabetes after transplantation (NODAT) is a frequent complication in kidney transplant (KT) recipients with unfavorable outcomes, although a nationwide study on epidemiology and clinical outcome of NODAT in Korean KT recipients remain rare.

Methods: We identified KT recipients by using a Health Insurance Review and Assessment Service of South Korea from the year of 2008 to 2017. We excluded patients with preexisting diabetes, multi-organ transplantation, and being progressed to graft failure less than 1 year after KT. NODAT was defined as consecutive 30 days prescription history of antidiabetic medication after KT. We analyzed the impact of NODAT on death censored graft failure (DCGF), death without graft failure (DWGF), and major adverse cardiovascular events (MACE) by time-dependent Cox analysis.

Results: Among a total of 16,719 KT recipients, 10,311 were included after exclusion. 19.8 percent of KT recipients were diagnosed with NODAT. The proportion of patients developing NODAT tended to increase over time, and 64% of NODAT was diagnosed within the first 6 months after KT. NODAT patients were older, more men, having longer pre-KT dialysis vintages, and being exposed more basaltimulin and more rejection episodes requiring high-dose steroids treatment after KT. During follow-up, 520 DCGF, 180 DWGF, and 213 MACE events were occurred. NODAT patients showed higher risks of DCGF (adjusted hazard ratio [aHR], 1.87; 95% confidence interval [CI], 1.52-2.23; p < 0.001), DWGF (aHR 1.77; 95% CI, 1.28-2.43; p = 0.001), and MACE (aHR 1.46; 95% CI, 1.08-1.96; p = 0.031) than patients without NODAT. Twenty-one percent of NODAT patients could be stopped their anti-diabetic medications after the diagnosis, although this did not affect the clinical outcomes.

Conclusions: About 20% of diabetes-naïve KT recipients were diagnosed with NODAT with a recently increasing pattern. NODAT in KT recipients affected worse graft and patients outcomes as well as MACE.

Funding: Government Support - Non-U.S.

PO2073

Association Between Early Post-Transplant Hypertension or Related Antihypertensive Use and Prognosis of Kidney Transplant Recipients: A Nationwide Observational Study

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Background: Additional research is warranted for the clinical significance of post-transplant hypertension and related antihypertensive medication usage in kidney transplant (KT) recipients.

Methods: This observational study included nationwide KT recipients who maintained functioning graft for at least 1 year after KT in South Korea during 2008 to 2017. The usage of antihypertensive medications between 6 months to 1 year was the main exposure, and those who had inconsistent/short usage of antihypertensive drugs were excluded. The primary outcome included death-censored graft failure (DCGF), death-with-functioning graft (DWGF), and major adverse cerebrocardiovascular events (MACCEs).

Results: We included 8014 patients without post-transplant hypertension and 6114 recipients who received treatments for hypertension in the post-transplant period. Those with post-transplant hypertension had significantly worse risk of DCGF than those without [adjusted hazard ratio (HR) 1.27 (1.09-1.48)]. Post-transplant hypertension patients who required multiple drugs showed significantly higher risk of DWGF [HR 1.57 (1.17-2.09)] and MACCE [HR 1.35 (1.01-1.81)] than the controls. Among the single-agent users, those who received beta-blockers showed a significantly higher risk of DCGF, although the risks of DWGF or MACCE were similar between the types of antihypertensive agents. Among the multiple agent users, the prognosis was similar regardless of the prescribed types of antihypertensive agents.

Conclusions: Post-transplant hypertension was associated with poor post-transplant prognosis, particularly when multiple types of medications were required for treatment. During initial prescription of antihypertensive medication, clinicians may consider that beta-blockers were associated with a higher risk of DCGF in the single-agent users.

The association between PTA and overall mortality

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Underline represents presenting author.
PO2075
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Background: Kidney transplantation recipients (KTR) with coronavirus disease 2019 (COVID-19) are at higher risk of death than general population. However, mortality risk factors in KTR are still not clearly identified. Our objective was to systematically analyze published evidence for risk factors associated with mortality in COVID-19 KTR.

Methods: Electronic databases were searched for eligible studies on 8 January 2021. All prospective and retrospective studies of COVID-19 in KTR were considered eligible without language restriction. Since data in case reports and series could potentially be subsets of larger studies, only studies with at least 50 patients were included. Random-effects model meta-analysis was used to calculate weighted mean difference (WMD) and pooled odds ratio (OR) of factors associated with mortality.

Results: A total of 56 articles retrieved, 10 were included in the meta-analysis comprising 1,778 KTR. Of these, 1,349 (76%) were survivors and 419 (24%) were non-survivors. Compared with survivors, non-survivors were significantly older (WMD 10.5 years, 95%-CI 9.0-12.0) and had shorter symptom onset before admission (WMD -1.3 days, 95%-CI -2.2 -0.3). KTR of deceased donor were at higher risk of death (OR 2.08, 95%-CI 1.03-4.20). Comorbidities including diabetes, cardiovascular disease, and cancer significantly increased mortality risk. KTR with dyspnea (OR 3.40, 95%-CI 2.51-4.66) and pneumonia (OR 3.61, 95%-CI 1.63-5.59) at presentation were at higher mortality. While diabetes decreased the risk (OR 0.69, 95%-CI 0.39-0.72). Acute kidney injury was associated with mortality (OR 1.74, 95%-CI 1.01-2.98). Inflammatory markers were significantly higher in the non-survivors, including lactate dehydrogenase, C-reactive protein, D-dimer, pro-calcitonin, and interleukin-6.

Conclusions: A number of COVID-19 mortality risk factors were identified from KTR patient characteristics, presenting symptoms, and laboratory investigations. KTR with these risk factors should receive more intensive monitoring and early therapeutic interventions to optimize health outcomes.

PO2076
Impact of Native Kidney Disease on Post-Transplant Cancer Development
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Background: Long-term risk of cancer development among patients with glomerulonephritis (GN) and congenital anomalies of the kidney and urinary tract (CAKUT) have been shown previously. However, the association between native kidney disease and de novo cancers after kidney transplantation (KTx) needed to be clarified.

Methods: We examined national Scientific Registry of Transplant Recipients (SRTR) data for patients underwent KTxs (2000-2021) to investigate the association of native kidney disease with de novo cancer diagnoses after KTxs. Patient with history of previous transplant and patients with history of cancer before KTXs were excluded. We identified KTxs recipients with hypertension (HTN) (n=68432), diabetes mellitus (DM) (n=79809), glomerulonephritis (GN) (n=54381), CAKUT (n=6508) and others (n=56048) as cause of native kidney disease.

Results: Compared with the reference HTN group, GN (aHR, 1.39, 95%-CI 1.31-1.48), CAKUT (aHR, 1.37, 95%-CI 1.33-1.41) and others (aHR, 1.32, 95%-CI 1.29-1.35) groups are also associated with higher risk of acute rejection within the 6 months post-KTx. Regarding graft failure, GN (aHR, 1.09, 95%-CI 1.05-1.13) and others (aHR, 1.08, 95%-CI 1.03-1.14) groups have significantly lower risk of 5 years all cause graft failure compared to reference group. However, the risk of death censored graft failure was significantly lower in DM (aHR, 1.09, 95%-CI 0.90-1.00) and others (aHR, 1.03, 95%-CI 0.95-1.11) groups.

Conclusions: Native kidney diseases, GN and CAKUT, have been associated with acute rejection and de novo cancers after KTXs. Immunosuppressive treatment and cancer screening may need to be modified according to native kidney disease.

PO2077
Effect of Cold Ischemia Time on Death-Censored Graft Survival of Post-One-Year Survivor Deceased Donor Kidney Transplant Recipients in the United States
Bhambidipati V. Murthy, Ahmed A. Awan, Abbas Rana, John A. Goss. Baylor College of Medicine, Houston, TX.

Background: Prolonged cold ischemia has been associated with increased incidence of delayed graft function and poor short term graft survival among deceased donor allografts. However, the data on long term graft survival is less clear. Our aim was to evaluate long-term graft survival for deceased donor kidney recipients who survived one year after transplantation such that the immediate adverse outcomes do not cloud the long term outcomes.

Methods: We retrospectively analyzed data from the United Network for Organ Sharing (UNOS) from 1995 to 2017. Living donor transplants, multi-organ transplants, recipients <18 years age at transplantation, and those who died within 1 year of transplantation were excluded. Using multivariable Cox regression analysis, a total of 145,680 recipients were analyzed with death censoring to estimate graft survival with varying cold ischemia times.

Results: Compared with cold ischemic time of <5 hours, the graft failure probability steadily increased with increasing cold ischemia time such that the hazards of graft loss were 42% higher with ischemic time greater than 35 hours (Figure 1). Worse graft survival was also observed in males (HR 1.08), increasing donor age beyond 30 years, Blacks (HR 1.77), BMI >30 (HR 1.13), those who had dialysis prior to transplant (HR 1.41), diabetes (HR 1.12), and PRA >90% (HR 1.16). Recipients older than 40 years had lower graft loss compared to those between 18 and 40 years age.

Conclusions: Prolonged cold ischemia time adversely affects long-term graft survival among deceased donor kidney transplant recipients in the US. The hazards of graft loss appear to be proportional to the duration of cold ischemia time.

Funding: Clinical Revenue Support

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Underline represents presenting author.
PO2078

Polygenic Burden for Intracranial Aneurysm and Hypertension in Deceased Kidney Donors Who Died of Intracranial Haemorrhage

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**Background:** A polygenic risk score (PRS) estimates the cumulative effect of common genetic variants on the risk of a disease. It is calculated by summing up all the effect alleles present in the individual, weighted by the effect size, as measured in a GWAS. Intracranial haemorrhage is a common cause of death among kidney donors, but limited research has been done to investigate polygenic burden for intracranial aneurysm (IA) and hypertension in deceased transplant donors.

**Methods:** Our data consisted of 2,122 genotyped donor-recipient pairs from the United Kingdom and Ireland Renal Transplant Consortium (UKIRCT) and 5,519 controls from the 1958 British Birth Cohort and UK Blood Service. We created polygenic risk scores for IA and hypertension using published GWAS summary statistics from 7,495 cases and 71,934 controls for IA and 76,666 cases and 206,305 controls for hypertension. We investigated the difference in PRS between the UKIRTC donors who died of intracranial haemorrhage (1,303 individuals) and the controls while adjusting for covariates of sex and the first 4 principal components.

**Results:** We found that the IA PRS explained 4.1% of the variance between case and control status (p-value: 9.6 x 10^-10). The odds ratio on the phenotype for those in the lowest demi-decile of the IA PRS was 0.42 (95% CI: 0.34-0.82) compared to 2.8 (1.9-4.0) for those in the highest demi-decile. Similarly, the PRS for hypertension explained 1% of the variance (p-value: 7.5 x 10^-5). The corresponding odds ratios were 0.68 (CI: 0.46-1.07) and 1.5 (1.1-2.3) for those in the lowest and highest demi-deciles respectively.

**Conclusions:** PRSs for IA and hypertension based on these data appear to explain 4% and 1% respectively of the variance in case-control status between kidney donors who have died of intracranial haemorrhage and controls. These observations could have utility in testing relatives of donors who died of intracranial haemorrhage to determine if they share the same risk for intracerebral haemorrhage and so if they may be useful in advising screening or other precautions to minimise their risk of intracerebral haemorrhage. These observations need to be confirmed in other cohorts. Further studies using similar approaches could investigate other causes of death among kidney donors.

**Funding:** Government Support - Non-U.S.

PO2079

Characteristics of Potential and Actual Living Kidney Donors: A Single-Center Experience

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**Background:** Living kidney donors contribute only 28% of all transplanted kidneys. Our study aimed to examine characteristics of potential compared to actual living kidney donors, in order to better understand barriers to successful donation.

**Methods:** We performed a retrospective analysis of 1,815 intake forms completed by kidney donor candidates from 2016-2018 at a single transplant center. We analyzed data from all potential donors who completed the intake until they became ineligible or withdrew, or, until donation was reached. Baseline characteristics were compared between potential and actual donor groups.

**Results:** The donation process was deconstructed into 5 steps. The percentage of potential donor drop out at each step and the most common reason for drop out are shown in Table 1. Of the 125 actual donors, 115 (94.5%) were white and 81 (64.8%) were female. A family member was more likely than an unrelated individual to complete the process. At the intake step 35.5% of potential donors identified as family of the potential recipient; at donation 72.7% were family, p <0.001. Most potential and actual donors were referred by the transplant candidate (56.0% and 43.5%, respectively). Social media networking was a larger contributor to the potential donor pool than a source for actual donors (16.5% in potential donors v 2.4% in actual donors, p <0.0001). There were no significant differences between potential and actual donor group with respect to substance use, marital status, level of education, and employment status.

**Conclusions:** Kidney donor interest is high in the early steps, but few donor candidates become actual donors. A family relationship increases the likelihood a potential donor will become an actual donor. There is a significant drop out of potential donors for candidates become actual donors. A family relationship increases the likelihood a potential donor will become an actual donor. There is a significant drop out of potential donors for candidates become actual donors. A family relationship increases the likelihood a potential donor will become an actual donor.

**Funding:** NIDDK Support

Table 1: LKD Candidate Drop Out by Donation Step

PO2080

Remnant Kidney Hypertrophy Is Negatively Associated with Albuminuria After Donor Nephrectomy

Masatomo Ogata, Takamasa Miyaiuchi, Kiyomi Osako, Maho Terasita, Naohiko Imai, Yugo Shibagaki, Masahiko Yazawa. St. Marianna University School of Medicine, Kawasaki, Japan.

**Background:** Glomerular ultrafiltration pressure in the remnant kidney remains after donor nephrectomy by the compensatory increase in the glomerular ultrafiltration coefficient, consisting of renal blood flow and cortex volume, namely compensatory hypertrophy. This compensation may be related to the protection for the newly or progressively incident albuminuria, a well-known predictor for kidney damage. To elucidate this theory, we analyzed the relationship between the percentage of change in the remnant kidney volume over 1-year post donation and albuminuria after donation.

**Methods:** This was a retrospective observational study, with 36 living donors who underwent nephrectomy at our hospital between 2011-2018. The mean age of the participants was 59±8 years and 72% of them were female. We reviewed the computed tomography before and 1 year after donation to calculate the change (% in remnant kidney volume and investigated the associations with absolute values and relative changes in urinary albumin to creatinine ratio (UACR) 1, 2, and 3 years after donation. Pearson’s correlation coefficients was used for the significance of association. This study is approved by Institutional Review Committee of St. Marianna University School of Medicine (No. 1574).

**Results:** Mean remnant kidney volume change percentage 1-year after donation was 24±8±0%. Although statistically non-significant, negative associations were suggested between the change in remnant kidney volume and both the absolute values of % and % change in UACR (Figure).

**Conclusions:** Although relationships between change in remnant kidney volume and albuminuria were statistically insignificant due to the small sample size and analysis for not a risk population, consistently negative associations would suggest the clinical significance. To assess the long-term safety of living donors, the focus might be on whether the remnant kidney can be hypertrophic by compensation.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
**PO2082**

**African American Kidney Donor Denial**

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**Background:** Previous studies have demonstrated that the rate of living kidney donation is lower in African American (AA) compared to the Caucasian population but whether this low donation rate is related to higher denial rates in AA donors is unclear. Comorbidities play a major role in live donors exclusions, especially hypertension and DM, which could affect the pool of potential donors. The aim of our study is to report the rates and causes of living kidney donor denial in our facility and to further stratify the exclusion rate based on race.

**Methods:** A retrospective cohort study of 439 denied candidates (age ≥18) who underwent evaluation for living kidney donation at our facility in the period from 2006 to 2014 was performed. Donors underwent a 24 hour ambulatory blood pressure monitor, 24-hour oral intake, 24-hour intravenous excretion and CT angiography as part of their donor evaluations. Reasons for denying donors were identified and grouped into 4 groups: 1) Low GFR, 2) Anatomical variation 3) Hypertension 4) Other causes.

**Results:** The cohort consisted of 84 AA, 304 Caucasian and 32 Hispanic donors. Hispanic donors were excluded from further analysis. AA donors were younger (P=0.01) compared to Caucasians. Day time and night time systolic and diastolic arterial blood pressure were comparable between AA and Caucasian (P=0.3 for all) Table 1 summarizes the different reasons for donor denial by donor race. There was no difference between AA and Caucasians or Hispanics in the reason for denial for donation.

**Conclusions:** In this limited study the reasons for denial of kidney donation was not different between AA and Caucasians. Given that the disparity remains, other causes for the low donation in the AA population should be explored and mitigated.

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<th>Potential Donor Characteristics</th>
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<td>Time average diastolic BP</td>
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**PO2083**

“I Just Don’t Trust It”: Exploring the Role of Mistrust in Shaping Living Donor Kidney Transplant Pathways for African, Caribbean, and Black communities in Toronto, Canada

Lydia-Joi L. Marshall, University Health Network, Toronto, ON, Canada.

**Background:** In Canada, African, Caribbean, and Black (ACB) patients with kidney failure are 40-70% less likely to receive a LDKT compared to Whites. To date, research has focused on individual factors, neglecting the impact of systemic racism in shaping ACB community attitudes toward LDKT. Further absent is Canadian research using qualitative methodologies.

**Methods:** We used an exploratory qualitative approach to understand perspectives and attitudes about LDKT in Canadian ACB communities. Using purposive and snowball sampling, we recruited 81 self-identified ACB community participants to take part in eight focus group discussions between January and November 2020. Participants were asked questions about their racial and ethnic identities, medical experiences and attitudes, and knowledge and perspectives on LDKT. We then applied a Critical Race analytical framework to analyze transcripts, focusing on the tenets of racial consciousness, social location, power dynamics, and countermovements.

**Results:** Of the 81 participants 63% was female, 46% were <50 years of age, 53% were immigrants to Canada. 36% self-identified as North American Black/African; 48% as Caribbean; 6% as North African; and 4% as Central/West African. Three key themes emerged from the data. First, we found that like in the U.S., participants expressed medical mistrust. Second, this medical mistrust was rooted in a combination of processes of racialization (medical racism), historical legacies of medical mistreatment, and lived negative experiences within the health care system. Lastly, medical mistrust informed health and illness related decision-making risk assessment, perspectives on LDKT, lack of engagement with traditional health care settings, and medical needs.

**Conclusions:** ACB community attitudes and decision-making processes about LDKT are complex, historically-rooted, and informed by broader medical mistrust. This suggests that broader systemic barriers to adequate health care outside of the LDKT pathway, may have far-reaching effects. Further research is needed to better understand how the broader medical experiences of ACB communities may be an underappreciated factor that shapes racial disparities in transplantation, and the kinds of interventions needed to facilitate broader access to LDKT.

**Funding:** Government Support - Non-U.S.

**PO2084**

**Employment Status and Work Functioning in Kidney Transplant Recipients**

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**Background:** Reliable employment figures of stable kidney transplant recipients (KTR) in Europe are lacking. Additionally, little is known about work functioning among employed KTR, and which clinical factors and (drug-related) side-effects are associated with work functioning.

**Methods:** We included 668 KTR of working age (59% male, age 51±11 years), at a median of 3 [IQR:2 to 10] years after transplantation, enrolled in the ongoing TransplantLines Biobank and Cohort Study (NCT03272841, Groningen, The Netherlands). Work and work-related functioning were assessed using the work role functioning questionnaire (WRFQ). Self-reported work ability was assessed using an item of the Work Ability Index (WAI). Results were compared to 246 (43% male, age 53±9 years) potential kidney donors used as healthy controls (HC).

**Results:** Employment rates were significantly lower among KTR compared to HC (56% vs. 79%, respectively, P<0.001). Employed KTR reported lower work functioning compared to employed HC (median [IQR] WRFQ total score: 94 [75 to 100] vs. 100 [83 to 100], P=0.026, Figure 1). Similarly, self-reported work ability was lower in KTR compared to HC (mean 7.6±1.9 vs. 8.6±1.5, P<0.001). Among KTR, fatigue was most strongly associated with working function, independently of potential confounders. Other parameters including anemia, blood albumin, use of beta-blockers, and neurological and mental drug-related side-effects were also independently associated with work functioning.

**Conclusions:** In our large representative population, only 56% of KTR in their working age were employed. In addition, employed KTR frequently experience impaired work functioning and have limited self-reported work ability. These results underline the individual and societal need to improve employment rates and work-related functioning among KTR. Fatigue, anemia, nutritional status, beta-blocker use, and drug-related side-effects may be potential targets, and should be further investigated.

**PO2085**

**A2 to B Deceased Donor Renal Transplantation Outcome Analysis: A Single-Center Experience**

Sandiya Bindrøo, Mona D. Doshi. University of Michigan, Ann Arbor, MI.

**Background:** A2 to B renal transplantation has been underused and significant knowledge gaps are noted in areas of rejections, infection rate, and anti-A titers thresholds post-transplant. The purpose of our study is to assess antibody mediated rejection (AMR) rates in A2 to B DDKT and determine association with anti-A IgG titers. We also assessed graft function, rejection and infection rates.

**Methods:** Retrospective chart review of 55 A2 to B DDKT performed at the University of Michigan from January 2015 to September 2020 was done. All patients received Thymoglobulin for induction and were maintained on triple immunosuppression. All patients underwent monitoring of anti-A2 titers and surveillance biopsy at 3, 6- and 12- months after transplant. Other outcomes included graft function, rejection and infection rates at last follow-up.

**Results:** Our cohort consisted of 55 recipients with mean age of 54.8±13 years, 67% males and 29% African Americans. The median follow-up time was 2.5 [0.5-5] years. Ten developed acute rejection at 3 [1-6] months after transplant. One patient developed hyperacute rejection due to ABO incompatibility, five developed T cell mediated rejection, and four had AMR due to donor specific antibodies (DSA) against HLA. Anti-A titters remained undetectable or less (< 1:4) in 98% patients in post-transplant period with no increase in titers at 3-6 month follow up. Anti-A titer increased to 1:128 in one patient with hyper acute rejection. Overall, 20% mortality was noted, unrelated to graft dysfunction at median follow-up of 1.8 [0.08-4] years. 20% post-transplant infections (bacterial, viral and fungal) accounted for 41% cases. BK viremia noted in 20% with BK nephrotoxicity in six. The mean (SD) glomerular filtration rate, creatinine and urine protein creatinine ratio at three months, one year and at last follow up post-transplant was 49 (14.69), 1.40(0.47), 0.32 (0.55), 54 (14.49), 1.3 (0.43), 0.17 (0.20) and 52.8 (14.69), 1.4(0.59), 0.22 (0.27) respectively.
Conclusions: Our study showed no overall increase in AMR due to ABOi in A2 to B DDKT and is the first study to assess AMR along with anti-A titers in A2 to B DDKT. More such studies are needed to assess anti-A trajectory with AMR. We also noted high infection and BK viremia rates, attributed to use of Thymoglobulin induction therapy. While A2B transplants have good graft outcomes, infectious complications are more frequent.

PO2086
A Successful Approach for A2 to B Cadaveric Renal Transplantation
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Background: Approximately 20% of blood group A individuals have reduced levels of A-antigen, termed A2, with less immunogenicity toward anti-A immunoglobulins. This allows the safe transplant of A2 kidneys into B or AB recipients. In 2014, the Kidney Allocation System was modified to encourage transplant centers to provide A2 kidneys for type B patients to reduce inequities in access. Studies have reported that rates of A2 to B transplants remain undervalued due to high rates of early acute rejection or thrombotic microangiopathy (TMA). We report on outcome metrics of A2 to B transplantation at the University of Texas Medical Branch (UTMB).

Methods: A retrospective, single center analysis of 29 patients who received A2 to B kidney transplants at UTMB between July 2015 and December 2020. We included stable (2 consents) and the first A-lgA titers ≥ 1.9 for A2 identified individuals. Anti-A titers were monitored quarterly in B waitlisted patients. All A2/A2 to B eligible recipients underwent pre-transplant volume exchange plasmapheresis, followed by 2 additional sessions on post-op days 1 and 3. Thymoglobulin was used for induction and steroids for maintenance immunosuppression.

Results: A major concern in A2 to B transplantation is the development of TMA or graft rejection. The incidence of rejection within the first year of all types of renal transplants ranges from 7.9% to 21.4%. We instituted an aggressive plasmapheresis protocol to reduce levels of potential pre-formed IgM anti-A antibodies that may induce graft failure. We report a rate of 3.4% for rejection or TMA within the first year of graft life which is less than previously published reports. This is due to pre- and post-transplant plasmapheresis in combination with intravenous immunoglobulin therapy. We elected not to follow anti-A titers levels post-transplant which did not result in higher rates of graft loss.

Conclusions: Our A2 to B transplant patients had a low rate of rejection and TMA demonstrating the efficacy of our triple maintenance immunosuppression protocol. Anti-A titers need not be followed post-operatively.

RESULTS

PO2087
Pneumocystis jiroveci pneumonia in Renal Transplant Recipients: Experience at a Tertiary Care Center
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Background: Pneumocystis jiroveci pneumonia (PJP) is an important cause of morbidity and mortality in post renal transplant recipients. Data on PJP in renal transplant recipients from India is lacking and we have attempted to address these lacunae.

Methods: This single center retrospective study included all cases of PJP in renal transplant recipients diagnosed at our institute. Demographic, clinical, laboratory and therapeutic outcomes of all these patients were analyzed.

Results: Of the 1870 renal transplant recipient records analyzed, 37 (1.9%) recipients were diagnosed with PJP. The median age of the patients was 38 years (17-74) with 31 males (83.8%). Three (8.1%) patients had deceased donors while 34 (91.9%) had living donors.

Conclusions: Our study showed no overall increase in AMR due to ABOi in A2 to B DDKT and is the first study to assess AMR along with anti-A titers in A2 to B DDKT. More such studies are needed to assess anti-A trajectory with AMR. We also noted high infection and BK viremia rates, attributed to use of Thymoglobulin induction therapy. While A2B transplants have good graft outcomes, infectious complications are more frequent.

PO2088
COVID-19 Infection in Kidney Transplant Patients: An Italian One-Year Single-Center Experience
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Background: COVID-19 is a life-threatening infection among elderly, comorbid patients, or transplanted patients. Lombardy (Region of Italy), accounts for 786,324 cases as of April 21st, 2021.

Methods: We retrospectively describe our single Centre experience in 82 adult kidney-transplant patients with COVID-19 infection during two pandemic outbreaks: 27 (first outbreak) and 65 (second).

Results: Thirty-seven patients were hospitalized (HP) and 65 were home managed (HM). Infection presented with fever (80%), cough (51%) and dyspnea (33%). HP were older (60±11 vs 50±14 years, p=0,001), had more severe respiratory symptoms (dyspnea 62.1%, VS p=0.001 – cough 67% p=0.008), and a longer length of disease (30±28 vs 21±10, p=0.04). Incidence of acute kidney injury (AKI) was 29.7% (p<0.0001). Steroid dosage was increased in 66% of patients, p=0.0003 while Calcineurin Inhibitors were reduced up to one third in 43% of cases, p=0.0001. Eleven patients died (13%). HM patients recovered completely without sequelae. In the overall cohort, AKI development (p=0.006 OR 50.4 CI 95% 3.0-836) and age (p=0.04 OR 1.1 CI 95% 1.0-1.2) were the most important factors influencing the probability of death during the infection.

Conclusions: Although we report a relatively low incidence of infection (5.1%) incidence of death is almost four times higher than in general population.

PO2089
The Impact of COVID-19 on Deceased Donor Renal Transplant Program in a Federal State of South India
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Background: The Covid-19 pandemic has had an impact on all facets of health care system, including organ donation, procurement and transplantation in many countries. India is the country most affected with covid 19 and also the country with a huge waiting list for all solid organ transplants. ESKD is unique that different forms of RRT are available to sustain life. The risk - benefit ratio for delaying elective transplantation during the pandemic is not clear.

Methods: A descriptive cross sectional study. All the deceased donor solid organ transplantations that took place in the state of Telangana from Jan 2020 to May 2021 were included. Live transplants were excluded. Comparison of the number of transplants of different organs, before and during the pandemic was done. Unpaired t test was used to compare the outcomes between the waitlisted and transplanted group.

Results: The total number of solid organ transplants from deceased donors in the pandemic year of 2020 dropped down to 54% compared to the previous year. Comparison between different organs revealed the maximum decline in number for kidney transplantation (51%), compared to liver (42%), heart (18%) as opposed to 110% increase in lung transplantation. Infectivity rate of covid 19 in the waitlisted group (top 50 in each blood group) registered for deceased renal transplantation is 0.16%. The infectivity rate in the transplanted group (deceased donor renal transplant) during the pandemic in the post transplant period of 6 months is 0.19%. The mortality rate of covid 19 between the two groups is also similar (0.04 in the waitlisted group and 0.06% in the transplanted group). The unpaired t test showed no statistical difference between the two groups.
Conclusions: There is a significant decline in the number of transplantations during the pandemic. Kidney is the most affected organ with a 10% decline. Lung transplantation had a 110% rise in numbers during the pandemic. There is no statistical difference of the infectivity rate and mortality rate of covid 19 between waitlisted group and transplanted group of deceased donor renal transplant during the pandemic.

PO2090
The Impact of COVID-19 on Kidney Transplant Listing and Referral on the Mexican-American Border

Background: Laredo, Texas is a city on the Mexican-American border in South Texas that ranked as the most affected area in the United States relative to population in terms of COVID-19 in January 2021. The hospitalization rate, the area’s total resources devoted to treating coronavirus patients, reached 45.8% and it averaged 229.9 cases daily per 100,000 citizens. We reviewed data early in the COVID-19 pandemic in May 2020 and later in May 2021 to evaluate whether the pandemic affected rates of referral and/or waitlisting.

Methods: Data was gathered from three dialysis clinics in Laredo, TX. The number of patients waitlisted or scheduled for living donor transplantation was determined early in the COVID-19 pandemic in May 2020 and later in May 2021. The number of patients referred for transplantation but not yet waitlisted was also obtained as well as the number of patients not referred both early in the COVID-19 pandemic in May 2020 and in May 2021.

Results: In May 2020, a total of 285 patients were available for analysis. 52 patients (18.2%) were waitlisted or scheduled for living donor transplantation. An additional 91 patients (31.9%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 140 (49.1%) were not referred. In May 2021, a total of 244 patients were available for analysis. 36 patients (14.8%) were waitlisted or scheduled for living donor transplantation. An additional 71 patients (29%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 135 (55%) were not referred.

Conclusions: There was a smaller percentage of ESRD patients waitlisted or scheduled for living donor transplantation in May 2021 than early in the COVID-19 pandemic in May 2020. There was also a smaller percentage referred but not waitlisted and a larger percentage not referred. The 3.4% decrease in patients waitlisted or scheduled for living donor transplantation may be a result of the high COVID-19 burden in Laredo, TX and the wariness to travel approximately 150 miles to the nearest transplant center. It is not known whether this decrease will have lasting implications on access to transplantation.

PO2091
Coronavirus Disease 2019 and Kidney Transplantation in Saudi Arabia
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Background: Kidney transplant services all over the world were severely impacted by the coronavirus disease 2019 pandemic. The optimum management of kidney transplant recipients with coronavirus disease remains uncertain.

Methods: We conducted a multicenter cohort study of kidney transplant recipients with coronavirus disease 2019 infection. The mortality rate of kidney transplant recipients with COVID-19 is significantly higher than the general population, indicating a need for effective treatment to minimize potential severe symptoms in this population. We sought to evaluate the efficacy of monoclonal antibody therapy in decreasing the severity of COVID-19 symptoms among our kidney transplant recipients.

Results: We included 130 kidney transplant recipients, with a mean age of 48.7±6.1 years. Fifty-nine patients were managed at home with daily follow-up utilizing a dedicated clinic, while 71 (54.6%) required hospital admission. Acute kidney injury occurred in 35 (26.9%) patients. Secondary infections occurred in 38 (29.2%) patients. SARS-CoV-2 antibodies testing was carried out in 84 patients, of whom 70 tested positive for IgG and/or IgM. Fourteen patients died (10.8%). A multivariable Cox regression analysis showed that age, creatinine at presentation, acute kidney injury, and use of azithromycin and/or IgM. Fourteen patients died (10.8%). A multivariable Cox regression analysis showed that age, creatinine at presentation, acute kidney injury, and use of azithromycin and/or IgM.

Conclusions: Despite kidney transplant recipients with coronavirus disease 2019 infection having higher rate of hospital admission and mortality compared to the general population, a significant number of them can be managed using a telemedicine clinic. Most kidney transplant patients seem to mount an antibody response following coronavirus disease 2019 infection, and it remains to be seen if they will have a similar response to the incoming vaccines.

PO2092
Vitamin D Status and SARS-CoV-2 Infection in a Cohort of Renal Transplanted Patients
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Background: Immunomodulatory and anti-inflammatory properties have been hypothesized for native vitamin D (nVD). Very little is reported about nVD and risk of SARS-CoV-2 infection (COV) in renal transplant (RTx). In a cohort of renal transplanted patients (RTxp) we retrospectively evaluated: a) nVD status in patients with (COV+) and without (COV-) COV infection; b) the impact of nVD status on severity of COV.

Methods: The study includes 61 COV+ in whom nVD status was available in the year before the infection, and 122 COV- matched 1:2 for age (53[45-64]years), gender (M=60.7%), RTx vintage (72[15-75]years), presence of diabetes (18%), arterial hypertension (85%) and cardiac symptomatic disease (3%). Renal function, 24-h proteinuria, mineral metabolism (MM) parameters were evaluated at 1, 6 and 12 months before COV whereas nVD status was considered as the mean 25-OH-VD levels at the same timepoints. Severity of COV was based on the need for hospitalization (HOSP+): 27[6/1, 44.3%] and death (D:1-6/1, 9.8%).

Results: a) nVD levels were significantly lower in COV+ than in COV- (19[12-26] ng/mL and 23[16-30] ng/mL, respectively, p=0.01). No differences in the other biochemical parameters were found. The COV discriminative power of nVD status was evaluated by ROC curve (AUC 0.61, 95% CI 0.54-0.68, p<0.01), with a value of 25-OHVD 23.9 ng/mL showing the best discriminative power (sensibility 72%, specificity 47%). 81 nVD levels showed a trend towards lower values in HOSP+COV+ than HOSP- COV+ (17[8-25] ng/mL vs 20[14-26] ng/mL) and in D-COV+ than D-COV+ (13[6-23] ng/mL vs 20[13-26] ng/mL), although these differences did not reach the statistical significance (p=0.1 and p=0.2, respectively).

Conclusions: With the limitations of the retrospective nature of the study and the small sample size, our data report that: a) COV+ showed lower nVD levels in the year preceding the infection compared to controls with similar main demographic features and comorbid conditions; b) No differences were found in renal function, proteinuria, and other MM parameters between the two groups; c) No association was found between nVD levels in the year preceding the infection and COV severity.

PO2093
Treatment with Monoclonal Antibodies Minimize Severity of COVID-19 Illness Among Kidney Transplant Recipients

Background: The mortality rate of kidney transplant recipients with COVID-19 is significantly higher than the general population, indicating a need for effective treatment to minimize potential severe symptoms in this population. We sought to evaluate the efficacy of monoclonal antibody therapy in decreasing the severity of COVID-19 symptoms among our kidney transplant recipients.

Methods: We reviewed 17 kidney transplant recipients who were infected with SARS-CoV2 and received treatment with monoclonal antibody therapy. All patients were on standard immunosuppression with Tacrolimus and Prednisone, and 88% were on Mycophenolate prior to COVID diagnosis, which was subsequently reduced or held for at least 2 weeks.

Results: Of the 17 patients reviewed, median age was 61 years (range 42 to 77 years), 47% were male, 59% were Hispanic, and 29% were African American. Additionally 94% had history of hypertension, 47% diabetes mellitus, 18% coronary artery disease, and median BMI was 28.8 (range 23.4 to 41.9). Eighteen percent were transplanted <1 year, 29% between 1-5 years, 24% 6-10 years, and the remaining >10 years. All patients had mild symptoms without evidence of hypoxia, and 94% received monoclonal antibody therapy within 7 days of diagnosis. Bamlanivimab 700mg was the most commonly administered agent at 59%, while 18% received Bamlanivimab 700mg and Etesevimab 1400mg. Casirivimab 1200 mg and imdevimab 1200 mg was used in 24%. Only 2 out of the 17 patients (11.8%) required hospitalization, and both were non-COVID-19 related reasons. Five out of 17 patients (29.4%) were evaluated in the Emergency Department but not admitted. All 17 patients (100%) recovered from their COVID-19 illness. There were no episodes of graft failure.

Conclusions: Our experience suggests that monoclonal antibody therapies may be beneficial in preventing severe COVID-19 in renal transplant recipients and possibly reduce the need for COVID-19 related hospitalization in this high risk population. However, larger studies are needed to confirm these findings.
PO2094
Antibody Response to SARS-CoV-2 mRNA Vaccines in Pediatric Kidney Transplant Recipients
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Background: In the general population, mRNA SARS-CoV-2 vaccines are highly efficacious and patients form an antibody to S1 subunit of the SARS-CoV-2 spike protein. Early reports suggest a decreased antibody response in immunosuppressed adult solid organ transplant (SOT) patients. However, the serologic response in adolescent SOT patients has not yet been characterized.

Methods: Kidney transplant recipients (KTR) at our center who received both doses of an mRNA SARS-CoV-2 vaccine had SARS-CoV-2 spike protein antibody presence evaluated 4-8 weeks after their second dose of the vaccine as part of routine clinical care. We utilized the Abbott chemiluminescent microparticle immunosay or Siemens Atellica IM SARS-CoV-2 IgG. Patients were characterized as vaccine responders or non-responders.

Results: Of 47 vaccine-eligible KTR in our program, 34 received both doses of a SARS-CoV-2 mRNA vaccine. Twenty-three patients had spike antibody titers obtained. The median age was 21.5 years and all except one were transplanted over 3 years ago. Twenty-two received Pfizer-Biontech vaccine and one received Moderna. Twelve patients (52%) had a positive spike antibody. Of those who responded, eight patients’ immunosuppression regimens included mycophenolate (mean dose 719 mg/m2/day), three were treated with azathioprine and one was not taking an antimetabolite due to EoV viremia. All non-responders were treated with mycophenolate (average dose 755 mg/m2/day). Three patients had prior COVID-19 infection, and all had a positive antibody response.

Conclusions: Our results suggest vaccine response in adolescent KTR is suboptimal and lower than the general population. However, 52% response rate is similar to that previously described in adult SOT patients. While our study is limited by small sample size and lack of standardized timing for measuring antibodies, it provides further evidence of lower immunogenicity to SARS-CoV-2 vaccination in SOT. Those who did not respond tended to have a higher average dose of mycophenolate and this supports further study of alternative antimetabolite dosing strategies around the time of vaccination or the potential utility of a third vaccine dose in SOT patients. At our center, efforts to continue characterizing antibody response of pediatric KTR are ongoing and we anticipate additional data in the coming months as vaccine eligibility expands to younger patients.

PO2095
A Tale of Survival: COVID-19, Disseminated Cryptococcus, and Cytomegalovirus Disease in an ABO-Incompatible Kidney Transplant Recipient
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Introduction: We present a rare case of Collapsing Focal Segmental Glomerulosclerosis (FSGS) in Covid-19 (COVAN), disseminated Cryptococcus and CMV infection in a kidney transplant recipient with dialysis dependent acute kidney injury and successful renal and critical illness recovery.

Case Description: 63yo black male with an ABO incompatible kidney transplant 8yrs ago, baseline creatinine (Cr) of 1.4 mg/dl with acute Covid-19 infection with presenting Cr of 5.5 mg/dl and nephrotic range proteinuria (5.9g/m2). Started hemodialysis on day 21 of the acute illness. Normal imaging, stable anti-ABO titers and transplant kidney biopsy with collapsing FSGS and ATN. Blood cultures ordered for persistent fevers were positive for Cryptococcus neoformis. Biopsy of painful drained skin of the left flank revealed variably sized yeast forms within the dermis consistent with cutaneous Cryptococcus. Treated with amphotericin B/fluconazole followed by fluconazole with clearance of fungemia, resolution of fever and improvement of skin lesions. Immunosuppression was continued with reduced dose of tacrolimus and prednisone 10mg/day. Antimetabolite was discontinued. Persistent weakness and diarrhea lead to testing for CMV with PCR at 51,000copies/ml, treated with IV ganciclovir with complete resolution of symptoms. Discharged home on maintenance dialysis with valganciclovir and fluconazole prophylaxis. He returned on day 70 of illness with a Cr of 1.2 mg/dl, a 24hour urine collection with a creatinine clearance of 28 ml/min and 2gms of proteinuria. Dialysis was discontinued due to renal recovery. At last clinic follow up, day 100 from diagnosis, Cr remains stable at 1.7 mg/dl off dialysis.

Discussion: Immune dysregulation in the setting of acute Covid-19 infection coupled with long term immunosuppression may have contributed to multiple opportunistic infections. Optimal approach for immunosuppression in KTRs with acute Covid-19 infection is still evolving. Our patient was successfully treated without stopping all immunosuppression. Our case underscores importance of having low threshold to test for various opportunistic infections even in the setting of active Covid-19 infection. While data on COVAN in KTRs is limited, our case shows potential for renal recovery even in a high immunologic risk kidney transplant recipient.

PO2096
Cytomegalovirus Infection in Renal Transplant Recipients: Incidence, Clinical Profile and Outcome
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Background: Cytomegalovirus (CMV) is one of the commonly encountered opportunistic infection following renal transplantation, usually seen in the first 6 months of transplant. CMV diseases, untreated has a mortality rate of about 90% however has good response with prompt detection and antiviral therapy. With the changing immunosuppressive regimen, variation in pattern and occurrence of CMV infection can be seen. We studied the incidence, clinical profile and outcomes of CMV infection in renal transplant recipients at our center.

Methods: 291 renal transplant recipients between 2014 and 2020 were reviewed, 27 patients who had CMV infection, diagnosed by CMV DNA detection with polymerase chain reaction were included in the study and their demographic details, clinical profile and outcome were noted and analyzed.

Results: Among the 291 renal allograft recipients, 27 patients had 34 episodes of CMV infection with an incidence of 9.27% with a mean follow up of 52.6 months. 37.1% received deceased donor renal transplant and 62.9% received live renal transplant. Mean age at transplant was 33.8yrs, 81.4% were males. 18.6% were females. rATG as induction was given in 11.1%, Basiliximab in 37.1% and 51.8% received no induction therapy, all of them received triple immunosuppression with steroid, tacrolimus and MMF as maintenance immunosuppression. PTDM was present in 33.4%. Valganciclovir prophylaxis post-transplant was given in 77.8% where as an 22.2% did not receive prophylaxis. 20.5% infections occurred in < 3months, 26.5% between 3-6 months, 11.8% between 6-12 months and 41.2% in >12months post-transplant. Symptomatic disease with fever, malaise and leucopenia was the most common presentation in 73.5% of patients and 26.4% had asymptomatic infection with leucopenia and transaminits. All patients received Ganciclovir for 14-21 days followed by oral valganciclovir for 90 days as treatment of infection episode. Patient survival and graft survival rate was 85.2% and 77.7% at our center.

Conclusions: Changing immunosuppressive regimen with early withdrawal of steroids. Newer use of valganciclovir prophylaxis has been associated with lower incidence and milder form of CMV disease in our population. There seems to be a change in the traditional risk factors for CMV infection which needs to be further studied.

PO2097
Resistant Cytomegalovirus After Kidney Transplant: Reduced Immunosuppression, High-Dose Valganciclovir, and Letermovir Prophylaxis Guided by T Cell Immunity Assessment
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Introduction: CMV infections resistant to available antivirals are associated with increased morbidity and mortality after kidney transplant.

Case Description: A 58 yo male with ADPKD underwent pre-emptive LURTx. IS included Thymoglobulin, followed by tacrolimus, mycophenolate (MMF), and prednisone. Ten days after completing 6 mos. of valganciclovir(VGCV) prophylaxis (ppx) for CMV D+R serostatus he developed malaise and fever; CMV PCR was 197,033 IU/ml. VGCV 900 mg BID was started and MMF reduced. CMV PCR declined to 1399 IU/ml after 6 weeks, but then plateaued. CMV resistance testing (VGCV treatment day 62) found wild-type and mutated virus (UL54 T503I mutation and UL97 H520Q mutation) with predicted resistance to ganciclovir and cidofovir, but susceptibility to foscarnet. MMF was stopped and VGCV was increased to 1350 mg BID (150% dose for GFP). Foscarnet was avoided due to risk of nephrotoxicity, lack of disease, and time from transplant. There was no significant leukopenia on VGCV. Over the next 2 months, CMV PCR decreased to several hundred IU/ml to Below the Limit of Quantification. Letermovir ppx was started (VGCV 1 day 85) and VGCV stopped 8 days later. CMV PCR remained negative to BLQ on letemovir. Low dose MMF was restarted. T cell immunity panel (Viracor) showed good CD8 (5.04%), but low CD4 (0.15%) response, suggesting CMV infection would recur without prophylaxis. The patient remains on letemovir ppx. Letermovir is a CYP3A inhibitor, and tacrolimus required 25% dose reduction. DSA is negative at 1 yr post-transplant; creatinine remains around 1.1 mg/dl. Letemovir is a new CMV selective antiviral with novel mechanism of action inhibiting the viral terminase complex in late stages of replication. It is approved for prophylaxis in HCT, active against resistant strains, and not associated with myelo or nephrotoxicity.

Discussion: Resistant CMV infection is a clinical challenge. While susceptibility to foscarnet was predicted in this case, it was avoided (nephrotoxicity). Instead, immunosuppression was cautiously reduced and higher-dose VGCV was tolerated well. Once CMV viral load was negligible, a newer agent with novel mechanism of action, letemovir, was used for prophylaxis. Letemovir has been continued based on a low level of anti-CMV CD4 response, predicting high-risk for CMV recurrence.
PO2098

Rare Oral Lesions from Cytomegalovirus in Kidney Transplant

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Introduction: Cytomegalovirus (CMV) infection occurs frequently with kidney transplant recipients and it can affect any segment of gastrointestinal tract, but intra-oral localization is exceedingly rare. We present an interesting rare oral lesion from CMV infection in kidney transplant recipient

Case Description: A 49-year-old male with a history of kidney transplant admitted with odynophagia, pancytopenia, neutropenic fever and new tongue lesion for two weeks. Examination showed a 3X3 cm elevated, adherent plaque. He has a history of resistant CMV viremia with failed therapy to low-dose valganciclovir, ganciclovir, and letomovir. He attained an undetectable CMV viral load with Foscarnet but it was complicated with acute renal injury, and he was transitioned to a high dose valganclovir. His CMV PCR was < 50 on admission and biopsy of the tongue lesion revealed a positive immunohistochemical stain for CMV. We held his Valcyte on admission and his pancytopenia improved with filgrastim. Repeat CMV PCR increased to 17,000 IU/mL. He refused Foscarnet and was restarted on oral valganciclovir (1350 mg twice daily) and topical cidofovir. Even with undetectable CMV at presentation, he was noted to have disseminated infection. Myfotric and Gengraf were held and discharged on prednisone alone. At 2-week follow-up, the lesion and its associated symptoms had resolved.

Discussion: The presentation of oral CMV infection is highly variable with mucosal erythema, painful deep ulcers, erosions, but elevated tongue lesion have rarely been reported in literature to our knowledge. Treatment options includes ganciclovir, valganciclovir, foscarnet, letomovir and cidofovir. Early diagnosis is important because CMV increases other opportunistic infection and allograft rejection. Saliva and periodontal packets serve as reservoirs for CMV infection and frequent monitoring of periodontal health is needed post-transplant.

3X3 cm elevated, adherent tongue lesions

PO2099

Use of Epstein-Barr Virus (EBV) Cytotoxic T Lymphocyte Therapy in a Kidney Transplant Recipient with EBV-Associated Smooth Muscle Tumors

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Introduction: Epstein-Barr virus (EBV) is commonly associated with malignancies in transplant recipients, the most frequent being Post-transplant lymphoproliferative disorder. A rare, yet distinct, oncological entity are the EBV-associated smooth muscle tumors (EBV-SMTs). We present the case of multiple, malignant EBV-SMTs in a 34-year-old kidney transplant recipient, and the use of Tabelecleucel (EBV cytotoxic T lymphocyte therapy) as a targeted therapy for these tumors.

Case Description: A 34-year-old female kidney transplant recipient presented with fatigue, anorexia, and nighttime chills. Subsequent lab analysis revealed lymphopenia, elevated creatinine, hypercalcaemia and high EBV viral load. PET scan revealed intensely avid FDG liver, splenic and lytic lesions of the left femoral head (Fig.1). Diagnosis of EBV-SMTs was confirmed by immunohistochemistry positive for smooth muscle actin, supporting smooth muscle differentiation (Fig.2), and confirmatory in situ hybridization for EBV-encoded RNA. Patient’s immunosuppression was switched from tacrolimus to sirolimus, and treatment was initiated with Tabelecleucel. At the time of the writing of this report, the patient has completed the first cycle of treatment with Tabelecleucel and preparing for a second cycle of treatment. The patient’s symptoms have improved significantly and creatinine, calcium and white cell counts have returned to baseline, EBV viral load fell from 4120 to 133 and PET scan showed stabilization of disease. We will continue to report on the patient’s progress.

Discussion: EBV-SMTs are rare tumors which can present in a variety of ways and are easily missed. They are typically aggressive, with a poor response to radiation and chemotherapy. Tabelecleucel is an EBV cytotoxic T lymphocyte therapy, primarily used in immunosuppressed and stem cell transplant recipients. Use in kidney transplant recipients is promising but requires further investigation to better understand optimal HLA matching of cell lines with recipients and allografts.

PO2100

Economic and Insurance Outcomes for Living Kidney Donors and Matched Comparators in Korea

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Background: Although studies have reported kidney donation’s adverse health outcomes, its socioeconomic impact on living donors requires further study.

Methods: We performed a retrospective observational cohort study including a matched control group. We included 1,285 living kidney transplant donors from seven tertiary hospitals and a matched control group consisting of the same number of health screening examinners with similar baseline clinical and socioeconomic status from 2003 to 2016. Changes in employment status and household income were identified from the linked claims database, which includes employment and economic status information. The outcomes were compared between the donor and matched control groups on an annual basis using multivariable logistic regression analyses adjusted for various clinicodemographic characteristics.

Results: The median ages of the donors and matched controls were 45 and 46 years, respectively; 44.6% of the sample was male. The living donors were at higher risk of being unemployed or struggling to maintain employment during the first two years after donation (e.g., first-year loss of employment, odds ratio (OR) 2.27 (1.55–3.33)); however, this situation did not persist, compared with the matched control group. The donors also showed significantly lower odds for improvement in economic grades [OR 0.57 (0.47–0.71)] or higher odds for deterioration in financial status [OR 1.54 (1.23–1.93)] than the control group in the first year and succeeding time periods.

Conclusions: Live kidney donors may suffer from poor employment or low economic status even after their altruistic donation. Whether an advanced reimbursement program can reduce these disincentives should be further evaluated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
**PO2101**

When Is a Second Kidney Transplant Lifesaving? Effect of Waiting Time on Mortality in a Retrospective Cohort Study Using Target Trial Emulation

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**Background:** The median kidney transplant half-life is 10 to 15 years, and because of the scarcity of donor organs and immunological sensitization of candidates for retransplantation, there is a need for quantitative information if, and when a second transplantation is no longer associated with a reduced risk of mortality compared to waitlisted patients treated by dialysis. Therefore we investigated the association of time on waitlist with patient survival in patients who received a second transplantation versus remaining on waitlist with continued dialysis treatment.

**Methods:** In this retrospective study we used data of 2346 patients from the Austrian dialysis and transplant registry merged with data from Eurotransplant who were waitlisted for second kidney transplantation during the years 1980 to 2019. The analysis was based on target trial emulation via a sequential Cox approach, in which each observed transplant allocation started a virtual trial mimicking a randomized trial via inverse probability weighting. The analysis was adjusted for recipient age and sex, year and duration of first transplantation, duration of dialysis, and time between first graft loss and initial joining date of the waiting list for the second transplantation.

**Results:** Second kidney transplantation showed an increased restricted mean survival time (RMST) at 10 years of follow-up compared to remaining on the waiting list (5.8 life-months gained, 95% CI 6.9 to 11.1). However, this survival benefit was diminished in patients with longer waiting time after first graft loss: RMST differences at 10 years of follow-up were 8.0 (95% CI 1.3 to 14.0) and 0.1 life-months gained (95% CI -14.3 to 15.2) for patients with a waiting time after first graft loss of less than one year, and eight years, respectively.

**Conclusions:** Based on these data we conclude that a second kidney transplant leads to prolonged patient survival compared to remaining waitlisted by treatment by dialysis, but that the survival benefit diminishes with longer waiting time. Nevertheless, the higher quality of life after transplantation could be an argument to favour retransplantation if a suitable donor organ is available.

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**PO2102**

Correlation Between CT Volumetric and Nuclear Renal Scans in Donors with Renal Asymmetry

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**Background:** The Organ Procurement and Transplant Network (OPTN) lists renal asymmetry as a relative contraindication to donation. Clinicians resort to nuclear medicine scans to address discrepancies in kidney size observed by computed tomography (CT) volumetric. Our study looked at the correlation between CT volumetrics and nuclear medicine scan in addressing renal asymmetry.

**Methods:** At a large US transplant center, 62 potential donors with discrepancies in kidney size underwent both CT volumetric and nuclear medicine renal scans. The concordance correlation between the CT scan and nuclear medicine scan results was determined separately for the right and left kidney.

**Results:** The donors were 52.2 years of age [IQR: 38.5, 61.7], 29.0% male, and 59.7% white. By CT, the right kidney was 45.5% and left kidney was 54.5% of the overall volume. On nuclear medicine scan, right kidney was 46.8% and left kidney was 53.3% (Table 1). The Pearson correlation coefficient was 0.59 for the right kidney and was 0.58 for the left kidney (Figure 1, 2).

**Conclusions:** Nuclear medicine seems to offer no advantage over CT volumetric and it adds to the overall time (30-60 minutes) and cost (~$1,587) of the donor evaluation process.

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**PO2103**

The Effect of Race Coefficients on Preemptive Listing for Kidney Transplantation


**Background:** Race coefficients of glomerular filtration rate estimation (eGFR) formulas may be partially responsible for racial inequality in preemptive listing for kidney transplantation. The objective was to determine whether differences in racial distribution of preemptively listed candidates are reduced by calculating eGFR irrespective of race.

**Methods:** The Scientific Registry of Transplant Recipients database was used to evaluate differences in racial distribution of preemptive listing before and after application of the MDRD and CKD-EPI race coefficients to all preemptively listed non-Black kidney transplant candidates (eGFR modulation). Non-Black patients who had a recalculated eGFR > 20 were removed from the preemptive group. Odds ratios of preemptive listing were calculated by race with Black as the reference before and after eGFR modulation. Variables known to influence preemptive listing were included in the multivariable model.

**Results:** Among 385,087 kidney-alone transplant candidates from January 1, 2010 to December 2, 2020, 118,329 (30.7%) were identified as preemptively listed (median [IQR] age 56 [45-64]; 57.7% male; 71.7% White, 19% Black, 7.8% Asian, 0.6% multi-racial, 0.6% Native American, 0.3% Pacific Islander). After eGFR modulation, non-Black patients with an eGFR ≥20 were removed. Compared to Black candidates, the adjusted odds of preemptive listing for White candidates decreased from 2.01 (CI 1.78-2.26; p<0.001) before eGFR modulation to 1.0 (CI 1.0-1.39; p=0.406) with the MDRD and 1.37 (CI 1.18-1.58; p<0.001) with the CKD-EPI equations after adjusting for race coefficients.

**Conclusions:** The racial distribution of preemptively listed candidates closely mirrored the distribution on the wait list when all races were subject to the Black race coefficients. Removing race coefficients in GFR estimation formulas may result in more equitable racial distribution of preemptively listed candidates.
Increased Frequency of Kidneys Allocated Out of Sequence by Organ Procurement Organizations

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Background: Allocation of deceased donor kidneys follows a ranked match-run list of potential recipients. Organ procurement organizations (OPOs) deviate from the mandated match-run in exceptional circumstances with unknown frequency.

Methods: Using SRTR data on all deceased donor kidney transplants (Ktx) in the US from 2015-2019, we identified cases where an OPO-initiated allocation exception occurred (Operational-OPO, Donor Medical Urgency, Expedited Placement). We examined the frequency of Ktx from these exceptions over time and characteristics of donors with kidneys placed out-of-sequence.

Results: From 2015-2019, 981 kidneys from 673 donors were transplanted via OPO-initiated allocation exception. These transplants (median KDPI 67, age 47 yrs) nearly doubled from 2015-2019: 153 kidneys in 2015 (1.5% of all Ktx) to 291 in 2019 (2.1%). 52 of 58 OPOs used this process at least once (median <1 per year), but 2 outlier OPOs accounted for 54% of the exceptions over 5 years [426 (43%) and 110 (11%), Figure 1]. Only 56% of transplant centers received any allocation-exception Ktx, with 2 centers receiving 26% [129 (13%) and 132 (13%)]. Donor kidneys placed via allocation exception had less favorable characteristics, but only 25% had KDPI<85% (Table 1).

Allocation exception Ktx went to recipients with 2 fewer priority points (median score: 4.3 vs. 6.3 in-sequence), equivalent to 2 less years of waiting time.

Conclusions: Two OPOs and a few Ktx centers are driving an increase in OPO-initiated exceptions in kidney allocation. Although kidneys placed out-of-sequence were lower quality, the majority did not meet the traditional threshold for marginal kidneys. Without monitoring, increasing pressure to improve organ utilization risks increasing out-of-sequence allocation potentially exacerbating disparities in access to transplantation.

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Poster

PO2105

Survival Time Gained by Kidney Transplantation Compared to Transplantation: Clinical - Allocation, Evaluation, Prognosis, and Viral Onslaughts

PO2106

Meta-Analysis of Association Between TCF7L2 rs7903146 and Risk of New-Onset Diabetes After Kidney Transplantation

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Background: Single nucleotide polymorphisms may influence the risk of development of new-onset diabetes after transplantation (NODAT), a post-transplant clinical complication that is often implicated in organ allofraft rejection and mortality. We performed a meta-analysis of association between TCF7L2 rs7903146 and risk of post-transplant diabetes mellitus.

Methods: A systematic search was conducted using PubMed and ScienceDirect electronic databases for studies published between January 2001 to January 2021. Case-control or cohort studies reporting association between NODAT (diagnosis based on American Diabetes Association [ADA] criteria) and TCF7L2 rs7903146 were included. MetaGeno was used for meta-analysis (random effects model). Pooled odds ratios with 95% confidence intervals were reported to evaluate the strengths of association.

Results: Two reviewers independently screened for articles. A total of six case-control studies were included for full-text review and quantitative analysis after screening for eligibility. Genotypic distributions were in Hardy-Weinberg equilibrium for included studies. All papers reported statistically significant association of TCF7L2 rs7903146 for risk of NODAT except for one study. There was moderate heterogeneity among studies (I2 = 60.6%). Pooled analysis revealed 51% odds of developing NODAT with TCF7L2 rs7903146 T allele (Allele Contrast Model: OR = 1.51, 95% CI 1.13 – 2.02, adjusted p = 0.03).

Conclusions: The present meta-analysis demonstrated association between TCF7L2 variant rs7903146 and risk of developing NODAT. This finding may have clinical implications for individuals undergoing kidney transplantation.

PO2107

A Case of Native BK Virus Nephropathy in a Lung Transplant Patient

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Introduction: BK virus nephropathy (BKVN) is an opportunistic infection that can lead to progressive kidney dysfunction. Classically described in the allograft of kidney transplant patients, it is increasingly recognized in native kidneys of other non-renal solid organ transplants (NRSOTs). Here we describe a patient with a history of lung transplant with native BKVN.

Case Description: Our 68-year-old woman with a history of bilateral lung transplant for idiopathic pulmonary fibrosis was referred thirteen months post-transplant for worsening renal function. Her creatinine slowly increased from a baseline of 0.6 mg/dL to 1.9 mg/dL. Work up revealed a serum BK virus PCR level of 28,381,300 copies/ml. Kidney biopsy revealed numerous tubular epithelial cells with enlarged nuclei and intranuclear inclusions (Figure A) which stained positive for SV 40 (Figure B). Her tacrolimus and sirolimus were already reduced by the lung transplant team. Mycophenolic acid was discontinued. She was started on monthly intravenous immunoglobulin, and so she was admitted for intravenous cidofovir. Her creatinine preceding cidofovir treatment was 3.2 mg/dL. Work up revealed a serum BK virus PCR level of 28,381,300 copies/ml. Unfortunately, after a total of 2.5 mg/kg of intravenous cidofovir, her creatinine worsened to 4.68 mg/dL with no significant change in BK viremia. Cidofovir was discontinued.

Discussion: Native BKVN is more common than previously recognized in NRSOTs. There is unclear guidance if lung transplant patients should be screened for BK viremia routinely, and there is a lack of safe and efficacious treatment options. This case adds to the growing literature of lung transplant recipients who develop native BKVN and the challenges of BKVN treatment beyond reduction of immunosuppression.
Late Presentation of JC Virus-Associated Nephropathy in a Renal Transplant Recipient
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Introduction: JC virus (JCV) is a Polyomaviridae family member. JC virus-associated nephropathy (JCVAN) is more common in renal transplant recipients in comparison to other organ recipients. We report a case of JCVAN presenting after fourteen years post-renal transplantation.

Case Description: A 65-year-old female with primary kidney disease attributed to chronic hypertension, who received a preemptive renal transplant in 2006. Postoperatively, her hospital course was uneventful, with a baseline creatinine of 1.1 mg/dL at discharge. Induction immunotherapy consisted of anti-thymocyte globulin, maintenance immunosuppression (IS) regimen consisted of triple immunotherapy with mycophenolate mofetil, tacrolimus, and low dose prednisone. Approximately 14 years after renal transplant, the patient’s renal function deteriorated with creatinine increasing from 1.55 mg/dL to 2.43 mg/dL. The patient underwent a renal biopsy, which revealed positive staining for JCV. In hospital day 10, she developed status epilepticus, MRI brain was negative for suspected thiamine deficiency with intravenous thiamine. She developed myoclonus and hypertonia. Benzodiazepines and ciprofloxacin were started with concern for sepsis, sulfonamide and gafapitazone with concern for calcineurin inhibitor toxicity. Within hours she developed cardiac arrest and was successfully resuscitated. CT head post arrest demonstrated diffuse cerebral edema and tonsillar herniation indicating devastating neurological injury. She was declared brain dead on hospital day 17. The CSF metagenomic testing panel later returned positive for JC virus.

Discussion: JC virus is unusual in renal transplant recipients. Risk factors include previous acute rejection episodes and male gender. Notably, this female patient had no proven previous episodes of acute rejection. JCVAN usually occurs within the first year post-renat transplant. However, the reported case was an older female diagnosed with JCVAN fourteen years following the living donor kidney transplant. The diagnosis of JCVAN is confirmed histologically by obtaining a kidney biopsy and the mainstay of management is reducing the degree of immunosuppression.

A Case of Unexplained Encephalopathy in a Kidney Transplant Recipient
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Introduction: Progressive multifocal leukoencephalopathy is a fatal demyelinating disease caused by the JC virus. Kidney transplant patients who are immunosuppressed are at higher risk of this infection.

Case Description: A 42 year old woman with CKD5 from FSGS who underwent a living donor kidney transplant 5 months ago, on immunosuppression with tacrolimus, mycophenolate and prednisone, presented with acute confusion, expressive aphasia and gait disturbance. Differentials included structural, infectious, metabolic and nutritional causes. A lumbar puncture and MRI brain were unremarkable. She was treated for suspected thiamine deficiency with intravenous thiamine. She developed myoclonus and hypertonia. Benzodiazepines and ciprofloxacin were started with concern for sepsis, sulfonamide and gafapitazone with concern for calcineurin inhibitor toxicity. Within hours she developed cardiac arrest and was successfully resuscitated. CT head post arrest demonstrated diffuse cerebral edema and tonsillar herniation indicating devastating neurological injury. She was declared brain dead on hospital day 17. The CSF metagenomic testing panel later returned positive for JC virus.

Discussion: This is a complex and unfortunate case of PML due to JC virus in a newly transplanted patient, highlighting the ability of opportunistic CNS infections to masquerade as a nutritional deficiency/drug toxicity and the challenges of pursuing advanced diagnostic work up beyond standard testing. Immunosuppression in kidney transplant recipients remains a double edged sword where tiling the fine balance in favor of over-immunosuppression can lead to catastrophic infectious complications.

Boron Exposure and Decreased Risk of Mortality in Kidney Transplant Recipients
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Background: In a search for potential modifiable factors to improve long-term outcome among kidney transplant recipients (KTR), we studied dietary patterns in the Blue Zones, and hypothesized that boron exposure is associated with improved long-term outcome in KTR.

Methods: We determined 24h urinary boron excretion using inductively coupled plasmaspectrometry in 693 stable KTR (57% male, mean age 53y), enrolled in the TransplantLines F&N Biobank and Cohort Study. Dietary intake was assessed using validated food-frequency questionnaires.

Results: Linear regression analyses showed that dietary intake of fruit, wine and nuts were key determinants of boron excretion. In contrast, boron exposure was positively associated with homocysteine and inflammation parameters. In total, 73 (32%), 47 (20%) and 30 (13%) patients died among the lowest, middle and highest tertiles of boron,
respectively (P < 0.001). Cox regression analyses showed that high boron excretion was strongly associated with lower risk of mortality, independent of age, sex, eGFR and history of cardiovascular disease (HR per doubling 0.51, 95%CI:0.40 to 0.66, P < 0.001, Figure), and other potential clinical and dietary confounders.

Conclusions: Boron may be an overlooked target to improve long-term outcome among KTR and potentially other patients, partly through suggested beneficial effects on inflammation, the methionine-homocysteine cycle, and ageing processes. Interventional trials are warranted to confirm the potential of dietary boron supplementation in KTR and other patient populations.

Funding: Clinical Revenue Support

PO2111

Disseminated Adenovirus Infection in a Kidney Transplant Recipient


Introduction: Adenovirus as an opportunistic pathogen can cause infections in immunocompromised hosts. Cases of disseminated adenovirus infection in renal transplant patients have been described to be detrimental.

Case Description: 28-year-old male with end stage renal disease from focal segmental glomerulosclerosis with 2 prior failed renal transplant on hemodialysis received a 3rd renal transplant from a deceased donor. Initially planned for thymoglobulin induction, was switched to Basiliximab due to anaphylaxis during thymoglobulin infusion. Patient received plasmapharesis, IV immunoglobulin and rituximab in view of his sensitized status and presence of donor specific antibodies with persistent elevated creatinine early post-transplant. Subsequent allograft biopsy showed Banff IB rejection. He was treated with steroids and Alemtuzumab. Patient was discharged, but was readmitted with high fever. Blood and urine cultures were negative. Respiratory viral panel was positive for Adenovirus. Due to persistent high fever, immunosuppression was minimized. Hydronephrosis was drained with the nephrostomy. Repeat allograft biopsy was performed for rising creatinine. Light microscopy revealed severe necrotizing tubulitis with numerous basophilic nuclear viral inclusions and extensive polymorphonuclear inflammation consistent with adenoviral nephritis. Immunohistochemistry confirmed positive nuclear staining for adenoviral antigens. Patient was found to have moderate pericardial effusion and bilateral ground glass opacities. He was treated with Cidofovir, IV immunoglobulin and reduced immunosuppression. Due to persistent allograft dysfunction, he was maintained on dialysis. At the time of this report patient continues to be on dialysis.

Discussion: Adenoviral infection in healthy individual is often self-limited, rarely requiring more than symptomatic treatment. However, in immunosuppressed individuals it can lead to severe multisystem disease. In this patient, adenoviral infection following robust immunosuppression for early severe allograft rejection led to severe injury to allograft and near fatal illness. A high level of suspicion and prompt treatment can help improve the patient outcome.

PO2113

A Rare Case of Adenovirus Interstitial Nephritis and AMR Within Two Weeks of Kidney Transplant

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Introduction: Adenovirus nephropathy is a rare but devastating complication of kidney transplant. We report a case of adenovirus nephropathy associated with AMR within two weeks of renal transplant.

Case Description: 56 year old African American male with ESRD secondary to FSGS with history of LDKTXP in 2010 complicated by recurrent FSGS, BK viremia and chronic TCMR resulting in allograft failure and return to hemodialysis. He underwent DDKTXP in April, 2021 with rATG induction. He was noted to have slow graft function, serum creatinine trended down to 2.58 on post-op day 7 however again started to rise associated with fever and fatigue. PCR for BKV, EBV, CMV, COVID 19, influenza A and B remained negative. Adenovirus DNA was detected in sputum, urine and blood on post-op day 13. The patient underwent allograft biopsy on post-op day 16 which revealed severe necrotizing interstitial nephritis consistent with adenovirus nephropathy and early AMR (diffuse C4d positivity in peritubular capillaries with mild to moderate peritubular capillaritis, c4d3, ptc1-2). MMP was held; he received 5 plasmapharesis sessions and total of 1.1 g/kg IVIGs. Cidofovir 1mg/Kg was started on alternate days. His course was complicated by anuric renal failure requiring return to hemodialysis. No evidence of donor associated ADV could be established.

Discussion: The case highlights the importance of distinguishing adenovirus interstitial nephritis from acute allograft rejection on biopsy. The case also highlights the dilemma of treating adenovirus interstitial nephritis and AMR concomitantly. Our patient has history of prior kidney transplant which is a risk factor for ADV infection. Viral infection of allograft predisposes it to rejection by stimulating various immune pathways
Pre-Transplant Hypoalbuminemia Is Associated with Lower Risk for Rejection Among Kidney Transplant Recipients

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Background: Serum albumin is a marker of health status. Hypoalbuminemia is a common complication among patients with end-stage renal disease. Many patients would have hypoalbuminemia before getting a kidney transplant. The association of hypoalbuminemia and early post kidney transplant outcomes is not well studied.

Methods: All adult kidney transplant recipients at our center between 01/01/2001 and 12/31/2017 who had serum albumin levels ≤30 days prior to transplantation were included. Categorized recipients into four pretransplant albumin levels: normal albumin (≥3.5-<4.0 g/dL, reference group), mild (≥3.5-<4.0), moderate (≥3.0-<3.5), and severe (<3.0). We looked at pre-transplant hypoalbuminemia and outcomes including length of stay after transplant, readmission within 30 days, delayed graft failure, need for re-operation related to transplant. We also looked for the rate of rejection, graft failure, and death within the first six months of transplant.

Results: 2807 patients were included in the study. Of those, 1224 were identified as normal, 992 with mild, 466 with moderate, and 125 with severe. Albumin groups differed by age (p<0.001), BMI (p=0.01), pre-transplant dialysis (p=0.001), cause of ESRD (p=0.001), and induction agent (p=0.001). The mild group was associated with -1.24 days less LOS (95% CI -1.73 to -0.75; p<0.001); and moderate by -0.82 day (95% CI -1.46 to -0.19, p=0.01) but not a significant difference in severe group, after adjustment of multiple confounding factors, compared to reference. There were no differences in the rate of DGF, re-hospitalization within 30 days across the groups. The moderate group was associated with a lower need for re-operation (HR: 0.39; 95% CI: 0.17 to 0.89; p=0.025). The severe group (HR: 0.54, 95% CI: 0.30-0.85; p=0.008) and severe (HR: 0.20, 95% CI: 0.06-0.65; p=0.007) groups were associated with a significantly lower rejection rate within six months compared to reference levels.

Conclusions: Our results suggest that the hypoalbuminemia is associated with a lower risk of acute rejections and some other complications, were also comparable compared to recipients with normal albumin levels. These findings may guide transplant providers in the selection of patients and anticipate and mitigate some of the post-transplant complications.

PO2116
Peripheral Arterial Disease and Risk of Infection-Related Complications After Kidney Transplantation

Background: Infection-related hospitalizations after kidney transplantation are a common complication associated with significant morbidity and increased healthcare costs. Peripheral arterial disease (PAD) is a common comorbidity associated with poor wound healing and frailty, and may be an unrecognized risk factor for serious infections.

Methods: We included adults who received a kidney transplant in the US between 2006 and 2016. We used Fine-Gray models to assess the relationship between PAD and the composite outcome of infection-related hospitalization or infection-related death within the first year after transplant, while accounting for the competing risks of non-infection-related death or graft failure. We evaluated for presence of interactions between PAD and specific factors including age≥60, diabetes, and donor type (living vs. deceased) for this outcome.

Results: Out of 108,133 kidney transplant recipients (KTRs), 22,442 experienced the composite outcome in the first year after transplantation. In adjusted models, PAD was associated with a 38% higher hazard of the primary outcome (95% CI 1.34-1.43)[Figure]. Statistically significant interactions were present between PAD and donor type and age category. In subgroup analyses, PAD was associated with a higher risk for the composite outcome in living donor KTRs and with slightly higher risk in younger vs. older KTRs.

Conclusions: PAD was associated with an increased risk of infection-related hospitalization or death in the first year after transplantation, especially in subgroups who traditionally may not be evaluated for PAD prior to transplant, such as living donor KTRs and younger populations. Better screening for PAD even in young populations may improve our ability to reduce the risk of complications post-transplant.

PO2117
Pegloticase for Uncontrolled Gout in Kidney Transplant Recipients: Provisional Data Report of a Multicenter, Open-Label, Efficacy and Safety Study
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Background: Kidney transplant (KT) recipients have a high prevalence and severity of gout. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and efficacy is not impacted by CKD stage. Immunomodulator co-therapy with pegloticase has improved treatment response rates over phase 3 monotherapy trials by attenuating anti-druẩng antibodies (ADAs). This ongoing Phase 4 trial (PROTECT NCT04087720) examines safety and efficacy of pegloticase in KT patients with uncontrolled gout (UCG).

PO2115
Medial Arterial Calcification and Transplant Outcomes
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Background: Medial arterial calcification, a disorder distinct from atherosclerosis, is common in ESRD and associated with poor outcomes. Since this lesion does not regress after renal transplantation, it may be associated with poor outcomes in these patients as well. This was tested in a retrospective cohort of females undergoing renal transplantation using breast arterial calcification (BAC) as a specific marker of medial arterial calcification.

Methods: We identified all females with renal transplantation (Tx) through 2017 with digital mammograms performed at this institution. Mammograms were examined for arterial calcification, which was quantified by summing the lengths of calcified arterial segments. BAC was considered present at Tx if present any time prior to Tx or within 1.5 years after Tx. BAC was considered absent if absent within one year before Tx and any time after Tx. Medical records were reviewed for graft loss, cardiovascular disease (CVD: myocardial infarction, amputation, stroke, or any revascularization), and risk factors.

Results: 132 patients were identified with qualifying mammograms, which were performed a median of 0.50 years from Tx date. Clinical follow-up ranged from 3-13 years after Tx (mean: 6.4, time to graft loss 1.3-9.4 years (mean: 3.9), and time to CVD event 0.3-7.9 years (mean: 4.1). Patients with BAC (n=58) were older (55 vs. 50, p=0.004), had more diabetes (55 vs. 35%, p=0.02), parathyroidectomies (16 vs. 1.4%, p=0.005), and somewhat more pre-Tx CVD (12 vs. 4.1%, p=0.10). Graft loss (14 vs. 2.7%, p=0.025) and new CVD (21 vs. 5.4%, p=0.014) occurred more frequently in patients with BAC. Somewhat more pre-Tx CVD (12 vs. 4.1%, p=0.10). Graft loss (14 vs. 2.7%, p=0.025) and new CVD (21 vs. 5.4%, p=0.014) occurred more frequently in patients with BAC. BAC remained an independent predictor of graft loss in a logistic model including age, sex, BMI, and new CVD (21 vs. 5.4%, p=0.014) but not a significant difference in severe group, after adjustment of multiple confounding factors, compared to reference. There were no differences in the rate of DGF, re-hospitalization within 30 days across the groups. The moderate group was associated with a lower need for re-operation (HR: 0.39; 95% CI: 0.17 to 0.89; p=0.025). The severe group (HR: 0.54, 95% CI: 0.30-0.85; p=0.008) and severe (HR: 0.20, 95% CI: 0.06-0.65; p=0.007) groups were associated with a significantly lower rejection rate within six months compared to reference levels.

Conclusions: Our results suggest that the hypoalbuminemia is associated with a lower risk of acute rejections and some other complications, were also comparable compared to recipients with normal albumin levels. These findings may guide transplant providers in the selection of patients and anticipate and mitigate some of the post-transplant complications.

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647
Methods: KT recipients with UCG (serum urate [SU]≥7 mg/dL, intolerance/inefficacy to urate lowering therapy, and ≥1 of the following: tophi, chronic gouty arthritis, a2 flares in past yr) and functioning KT graft (eGFR≥15 mL/min/1.73m2) on stable immunosuppressive (IMS) therapy are included (KT≥1 y earlier). Pegloticase (8mg q2w for 24wks) safety and efficacy are examined. Primary endpoint was SU response (SU<6 mg/dL for ≥80% of time). Health Assessment Questionnaire (HAQ) pain (most severe: 100) and Disability Index (HAQ-DI) scores (max: 3) were evaluated.

Results: 20 patients enrolled (meansSD; age: 53.9±10.9 y, time since KT: 14.7±6.9 y, SU: 9.4±1.5 mg/dL, gout duration: 8.4±1.6 y; all on ≥2 IMS). At the time of analysis, 10 patients completed treatment, 3 discontinued pegloticase, 2 met SU monitoring rules (pre-dose SU>6 mg/dL at 2 consecutive visits) and discontinued pegloticase, and 5 were ongoing. All patients experienced initial substantial reductions in SU, which was maintained in the majority: 2 patients met monitoring rules. At week 24, no notable eGFR changes were observed. In patients that completed treatment, HAQ-pain and HAQ-DI scores improved by 26.7±30.3 (baseline: 35.9±30.2) and 0.2±0.5 (baseline: 1.0±1.0), respectively, at Week 24 (n=10). 7 SAEs (2 cellulitis, duodenal ulcer, sepsis, a-fib, diverticulitis, and localized infection) deemed unrelated to pegloticase, were reported in 5 patients. No anaphylaxis or IR events have occurred.

Conclusions: Preliminary results from the PROTECT trial, with Fall 2021 completion, demonstrate substantial and sustained SU decrease in the majority of KT recipients with uncontrolled gout. These findings are consistent with other reports on the effect of immunomodulation use with pegloticase.

Funding: Commercial Support - Horizon Therapeutics plc

PO2118
Discontinuation of Renin-Angiotensin System Blockade Among Kidney Transplant Recipients
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Background: Cardiovascular disease is common among recipients of kidney transplantation and is associated with high morbidity and mortality. While recent studies have shown evidence of cardiovascular benefit with the continuation of renin-angiotensin system (RAS) blockade for transplant-naïve patients with CKD there are little data on whether cessation of RAS blockade among kidney transplant recipients has kidney, cardiovascular, or survival benefits (or risks).

Methods: We performed a retrospective cohort study of kidney transplant recipients from the FAVORIT study. We included participants enrolled in the US who received an ARB or ACEi by self-report at one or more FAVORIT visits and performed a propensity score (PS) weighted Cox survival analysis to examine the risks or benefits of RAS discontinuation (vs. continuation). Outcomes were risk of death, return to dialysis, and major adverse cardiovascular events (MACE; stroke, myocardial infarction, coronary revascularization, or heart failure). Doubly robust estimation was also used on the PS weighted sample to provide conservative estimates.

Results: 2,009 US participants had at least one visit where they reported taking a RAS inhibitor. 30% (n=598) of participants discontinued RAS blockade. Compared to those who continued RAS blockade, participants who discontinued RAS blockade were significantly less likely to experience mortality, return to dialysis, and MACEs (Table). Hazard of adverse outcomes for kidney transplantation recipients discontinuing vs. continuing ACEi/ARB

* Adjusted for age, sex, transplant type, PRA, presence of diabetes, presence of cardiovascular disease, and type of maintenance therapy. PE analysis was adjusted only for age given low number of events (22)

PO2120
AV Fistula Leading to High-Output Cardiac Failure in a Kidney Transplant Population: Our Experience
Yahya R. Ahmad, Hasan Fattah. University of Kentucky, Lexington, KY.

Background: Among kidney allograft recipients, cardiovascular death continues to remain the major cause of mortality. Arteriovenous (A V) fistula is the optimal access for cardiac and renal physiology and improve quality of life. Early diagnosis and management is crucial as it can prevent irreversible changes in heart failure exacerbation after A V fistula closure, up until writing this data. We herein reviewed our center cases of high cardiac-output cardiac failure due to A V fistula and performed a retrospective study on kidney transplant recipients with a diagnosis of high output cardiac failure confirmed on right heart catheterization.

Methods: Retrospective chart review was performed on kidney transplant patients who had a diagnosis of high output cardiac failure confirmed on right heart catheterization and required AV fistula ligation for symptomatic high output cardiac failure at University of Kentucky.

Results: A total of 595 kidney transplants were performed at University of Kentucky during the study period (January 2015 until May 2021). 19 patients underwent fistula ligation, 7 of them (36.8%) required AV fistula ligation due to high output cardiac failure. Average peak blood flow across the AV fistula that required ligation was 2.8 L/min. Cardiac catheterization showed drop in cardiac output (CO) with AV fistula closure as seen in Figure 1. Improvement in renal functions was notable in most cases as seen in Figure 2. Symptoms of heart failure improved in all 7 patients with no re-admissions for heart failure exacerbation after AV fistula closure, up until writing this data.

Conclusions: High output heart failure from AV fistula is an underrecognized entity. Early diagnosis and management is crucial as it can prevent irreversible changes in cardiac and renal physiology and improve quality of life.

PO2119
Blood Transfusion and Venous Thromboembolism in Kidney Transplant Patients
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Background: Receipt of a red blood cell transfusion (RBCT) is common in kidney transplant patients and could have pro-thrombotic effects predisposing to venous thromboembolism (VTE). The aim of this study is to examine the risks for the development of VTE associated with the receipt of RBCT in kidney transplant patients.

Methods: We conducted a retrospective cohort study of all adult kidney transplant recipients at The Ottawa Hospital from 2002 to 2018, using administrative databases and medical chart review. The exposure of interest was receipt of a RBCT after transplant. Cox proportional hazards models were used to calculate hazard ratios (HR) for venous thromboembolism (VTE) [deep venous thrombosis (DVT) or pulmonary embolism (PE)] using RBCT as a time-varying, cumulative exposure.

Results: Out of 1,258 kidney transplant recipients, 468 (37%) received a total of 2,373 RBCT after transplant (incidence of 33 RBCT per 100 patient-years). During follow up, 79 study participants (6.3%) developed VTE, 72 had a DVT (5.7%) and 22 had a PE (1.8%). For the receipt of 1, 2, 3-5 and >5 RBCT, compared to individuals never transfused, the number of events and adjusted HR (95% CI) for VTE was 6 events (6.2%) HR 1.57 (0.69 to 3.58), 9 events (7.6%) HR 2.54 (1.30 to 4.96), 15 events (11.9%) HR 2.73 (1.38 to 5.41) and 23 events (18.1%) HR 5.77 (2.99 to 11.14) respectively; for DVT it was 6 events (6.2%) HR 1.94 (0.84 to 4.48), 9 events (7.6%) HR 2.92 (1.44 to 5.94), 14 events (11.1%) HR 3.29 (1.63 to 6.65) and 21 events (16.3%) HR 6.97 (3.53 to 13.76), respectively. For PE, among transfused individuals there were 14 events (3.0%) and the HR was 2.40 (1.02 to 5.61).

Conclusions: The risk for developing VTE, DVT and PE was significantly associated with the receipt of a RBCT in kidney transplant patients. Receipt of a RBCT should prompt considerations for judicious monitoring and assessment for possible thrombosis.
PO2121

Kidney Graft Ultrasound (US) After Elective JJ Stent Removal (EJJR)

PO2122

Hypophosphatemia in the Context of Hematopoietic Stem Cell Transplantation: An Underappreciated Complication

PO2123

A Cardiac Magnetic Resonance (CMR) Study with Native T1 Mapping in Patients Listed for a Kidney Transplant

Background: Hypophosphatemia (and hypokalemia) occur frequently in the context of hematopoietic allogeneic stem cell transplantation (allo-SCT) and during autologous SCT (auto-SCT) and have been attributed to uptake of these electrolytes by the reconstituting bone marrow. Similar metabolic complications can also occur after chemotherapy and during stem cell mobilization prior to auto SCT. These metabolic abnormalities have not been well described in the nephrology literature and in current textbooks of onco nephrology. Aim of the research was to describe the clinical course of patients with these electrolyte abnormalities in the context of SCT, chemotherapy and after bone marrow stimulation prior to SCT harvesting.

Methods: Chart review of patients undergoing SCT, after chemotherapy and SCT for harvesting.

Results: We identified 42 patients with 67 episodes of hypophosphatemia and hypokalemia. The clinical features and course are provided in the table.

Conclusions: Besides uptake of phosphorous and potassium by the reconstituting bone marrow under the stimulation of granulocyte colony a stimulation factor, other factors contributing to these metabolic abnormalities include poor oral intake, the use of phosphate binders, diuretics and losses during renal replacement therapy.

Background: Improving kidney transplant (KTx) outcomes remains a primary challenge and KTx ureter JJ stenting has been used to prevent urological complications. KTx US is an essential diagnostic tool to monitor patients with a complication, 3 required a surgical approach, 2 had a drainage inserted, 6% grade II UTD. 5% grade III UTD. Of the 123 complications detected: 41.4% had a newly diagnosed collection and 21% had urinary tract ectasia was not considered pathological. Of those with an US, 45.1% (123) had a comparison detected: 41.4% had a newly diagnosed collection and 21% had urinary tract dilatation (UTD): 10% grade I UTD, 6% grade II UTD, 5% grade III UTD. Of the 123 patients with a complication, 3 required a surgical approach, 2 had a drainage inserted, 2 nephrostomies, 11 required admission without surgical intervention and 51 had US follow up. Cumulative frequency analysis of complications post EJJR showed the highest diagnostic yield of US imaging was around day 10 post removal (figure 1).

Conclusions: Routine US after EJJR allowed timely diagnosis and early treatment of urological complications, a key factor for successful transplantation. KTx US is an effective, cheap and reproducible test that provides crucial information to guide clinical decisions, being most effective when performed 10 days post stent removal. Interventional nephrologists could do this examination promptly.

PO2122

Kidney Graft Ultrasound (US) After Elective JJ Stent Removal (EJJR)

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Background: Improving kidney transplant (KTx) outcomes remains a primary challenge and KTx ureter JJ stenting has been used to prevent urological complications. There is no consensus about EJJR timing, and literature regarding routine US imaging after EJJR to detect complications is lacking.

Methods: We retrospectively analysed all routine KTXs US done in our Unit from 2016-2020 by an experienced interventional nephrologist. US post EJJR findings were compared with previous US. KTXs characteristics, treatment and outcomes were recorded. We aimed to define incidence of urological complications diagnosed, US utility and best time interval to perform it.

Results: 345 KTXs were done: 62.9% were male receptors, 81.7% had a first KTX and 91.5% of the organs were from a deceased donor. No routine US post EJJR was done 20.9% due to COVID pandemic. Mean timing to elective JJ stent removal was 36.4 ± 25 days (SD). Mean time from EJJR to US was 16.3 ± 28.8 days (SD). Urinary tract ectasia was not considered pathological. Of those with an US, 45.1% (123) had a complication detected: 41.4% had a newly diagnosed collection and 21% had urinary tract dilatation (UTD): 10% grade I UTD, 6% grade II UTD, 5% grade III UTD. Of the 123 patients with a complication, 3 required a surgical approach, 2 had a drainage inserted, 2 nephrostomies, 11 required admission without surgical intervention and 51 had US follow up. Cumulative frequency analysis of complications post EJJR showed the highest diagnostic yield of US imaging was around day 10 post removal (figure 1).

Conclusions: Routine US after EJJR allowed timely diagnosis and early treatment of urological complications, a key factor for successful transplantation. KTX US is an effective, cheap and reproducible test that provides crucial information to guide clinical decisions, being most effective when performed 10 days post stent removal. Interventional nephrologists could do this examination promptly.

PO2123

A Cardiac Magnetic Resonance (CMR) Study with Native T1 Mapping in Patients Listed for a Kidney Transplant

Jordana Yahy,1 Sadeer Al-Kindi,2 Scott E. Janus,2 Aparna Padiyar,2 Mahboob Rahman,1,2 Sanjay Rajagopalan,1,2 Anne M. Huml,1,3 Mirela A. Dobre,2,3 Cleveland Clinic, Cleveland, OH; 1University Hospitals, Cleveland, OH; 2Case Western Reserve University, Cleveland, OH.

Background: Uremia causes activation of cardiac fibroblasts, a decrease in capillary density and promotes fibrosis by impairing oxygen diffusion to cardiomyocytes and promoting apoptosis. Assessment of myocardial fibrosis can be done non-invasively by non-contrast CMR T1 mapping. Though reversal of myocardial fibrosis post kidney transplant has been postulated, no study has systematically assessed it in transplant recipients compared to patients who remain on the waiting list. We aimed to assess the change in T1 maps post transplant in comparison to that in waitlisted patients.

Methods: Patients from 2 clinical sites, scheduled to receive a living kidney transplant underwent a non-contrast CMR prior to and 9 months post-transplant. An age-, sex-, race- and dialysis vintage-matched control group was selected from the patients waitlisted for a deceased donor, and had non-contrast CMR performed at baseline and after 9 months. Cardiac fibrosis measured by T1 maps were compared between the 2 groups.

Results: A total of 34 patients underwent CMR at study baseline. Mean age±SD was 55±14 years, and 13 (38%) were women, 7 (21%) Black and 16 (47%) were on dialysis. There was no difference in baseline T1 level in pre-dialysis (1063±50 ms vs dialysis (1062±51 ms) participants, and in transplant (1063±60 ms) vs waitlisted (1063±48 ms) participants. In multivariable adjusted models, age, diabetes, and heart failure were significantly associated with T1 levels. In a subgroup of 7 participants with available follow-up CMR, compared to control group, those transplant had a reduction in T1 levels (-64±59 ms vs +20±49 ms, p=0.09) Figure. Participants with high baseline T1 had the least decline in follow-up T1 levels.

Conclusions: Myocardial fibrosis as measured by native CMR T1 maps is reduced post kidney transplantation and continues to worsen for patients who remain actively listed for a transplant.

Funding: Private Foundation Support.
PO2124

SGLT-2 Inhibitor Treatment in Renal Transplant Recipients: A Single-Center Experience
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Background: Dapagliflozin, a sodium glucose transport protein 2 inhibitor (SGLT2-i), was recently approved for use in chronic kidney disease patients regardless of the presence of diabetes, after studies demonstrated improved renal and cardiovascular outcomes even in the absence of diabetes. The use of SGLT2-i in transplant recipients have been limited due to concerns for acute kidney injury (AKI) resulting from volume depletion or urinary tract infections (UTI) or other genital infections due to their glucosuric effect.

Methods: Retrospective review of all adult renal transplant recipients transplanted at our center between January 2013 and June 2020.

Results: 22 adult renal transplant patients at our center received treatment with an SGLT2-i during the study period. The patient’s ethnicity was representative of our patient’s population with 45% being Hispanic and 40% black. 68% of the patients were men and the median age was 64 years old. The vast majority of patients, 77%, had diabetes mellitus as the etiology of ESRD. 73% received a deceased donor kidney transplant and were started on SGLT2-i at a median time of 38 months post-transplant. 13 patients were treated with empagliflozin with a starting dose of 10mg daily, 7 with canagliflozin at 100mg daily, 1 dapagliflozin at 5mg daily, and 1 ertugliflozin at 2.5mg daily. The median creatinine at the start of treatment was 1.1mg/dl, urine protein creatinine ratio was 206 mg/g, and A1C 8.6%. SGLT2-inhibitors were well tolerated without significant adverse events. 4 patients developed hypoglycemia. Two patients developed a UTI and only 1 patient developed AKI requiring discontinuation of the drug. The median creatinine one-year post treatment initiation was stable at 1.1mg/dl, UPCR was 448.4 mg/g, and A1C was 7.7.

Finally, there was no significant interaction with the immunosuppression medications. The tacrolimus level remained stable and the patients did not require dose modifications post therapy initiation.

Conclusions: Treatment with SGLT2-i was well tolerated in our transplant population. Larger prospective studies are required to evaluate clinical outcomes in this patient population.

PO2125

Immunosuppression and Incident Cancer Risk in Older Kidney Transplant Recipients
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Background: Cancer is a serious complication after kidney transplant (KTx), especially among older adults. The relationship of immunosuppression (ISSx) to cancer in older KTx recipients is not well described.

Methods: We examined USRDS data (2005-2017) to explore associations of ISSx and cancer incidence in older KTx recipients (aged >65 years old) with new-onset cancer diagnoses >6 mo-to-5 yr post-KTx among Medicare-insured older (aged ≥65) adults. We used multivariate Cox regression models, IL2rAb+triple ISSx was associated with lower skin cancer risk (aHR, 0.600.760.96 of SGLT2-i), was less common with CsA-based ISSx (10.9% vs 14.7%; P=0.03) (Fig. A). In adjusted models, IL2rAb+triple ISSx was associated with lower skin cancer risk (aHR, 0.600.760.96). IL2rAb+steroid avoidance was associated with increased non-viral driven/non-skin cancer (aHR, 2.27±0.22), while CsA-based ISSx predicted lower risk (aHR, 0.72±0.41) (Fig. B). However, adjusted for time-varying impact of viral-driven (aHR, 2.27±0.22) and non-viral driven/non-skin cancers (aHR, 0.72±0.41), CsA use (aHR, 1.24±0.51) predicted increased mortality in older recipients.

Conclusions: Although CsA-based ISSx appears beneficial for non-skin cancer risk in older KTx recipients, this regimen is associated with increased mortality. Cancer risk is a consideration in tailoring ISSx in older KTx recipients.

Funding: NIDDK Support

PO2126

Belatacept Conversion in Proteinuric Kidney Transplant Recipients: Data from a Retrospective Cohort and a Prospective Trial
Orhan Efi,1 Ayman Al Jurdi,2 David Wojciechowski,1 Kassem Safa,1 Hannah M. Gilligan,1 Anil K. Chandraker,1 Jamil R. Azzi,1 Astrid Weins,2 Leonardo V. Riella.1 Massachusetts General Hospital, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Proteinuria is a strong predictor of graft loss in kidney transplant (KT) patients. Treatment options for proteinuria are limited to ACEIs/ARBs. Belatacept targets B7-1 which is also expressed on podocytes and has been linked to proteinuria by inducing podocyte migration. We examined the utility of belatacept conversion in proteinuric KT recipients.

Methods: In the phase I multicenter trial, we recruited EBV IgG+ adult KT recipients >6 months post-KT with an eGFR > 30ml/min/1.73m2, proteinuria > 1g/day on CNI-based immunosuppression. Patients were converted from CNI to belatacept. The primary outcome was 25% reduction in proteinuria in 12 months. In the retrospective cohort, we included patients who were converted to belatacept in 2015-2019.

Results: In the retrospective cohort, 12 of 77 belatacept conversion patients had pre-conversion proteinuria > 0.4 g/g and follow up values. Baseline proteinuria decreased from 1.0±1.9 g/g to 0.69±0.9 g/g at >12 months (p=0.070). Mean eGFR increased from 37±12 to 49±15 ml/min/1.73m2 at 12 months. In the prospective cohort, 15 KT recipients were recruited. At 12 months post-conversion, mean (±SD) eGFR remained stable at 43.7±12.9 ml/min/1.73m2 and proteinuria improved from 2.5±1.9 i to 1.7±1.8 g/g (p=0.068). Primary outcome was reached in 53% of the patients. None of the patients had graft rejection in the first year. One patient had worsening of proteinuria and discontinued belatacept. At 24 months, eGFR remained stable and proteinuria was 1.4±1.2 g/g. Figure 1 summarizes eGFR and proteinuria course from both cohorts.

Conclusions: Belatacept conversion in proteinuric KT recipients was associated with stable allograft function and reduction in proteinuria at 1 year and beyond.

Funding: Commercial Support - Bristol Myers Squibb
PO2127
Outcomes of Thymoglobulin vs. Basiliximab Induction Therapies in 2DR Mismatch Living-Donor Renal Transplant Recipients
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Background: 2DR HLA mismatch indicates a high immunological risk of renal transplant. Induction therapy with Thymoglobulin and Basiliximab result in a marked reduction of acute allograft rejection rate and improve graft survival. However, the outcomes in 2DR HLA mismatched renal transplant recipients (RTxRs) in the tacrolimus era remain understudied.

Methods: Using data from UNOS, all 2 DR mismatched RTRs who were maintained on tacrolimus and mycophenolate mofetil immunotherapy between September 2017 and September 2019 were included. Follow-up data was until September 2020. Patients who received transplants from living donors were included in the study. Collected data included recipient (age, sex, ethnicity, diabetes, body mass index), transplant (delayed graft function, cold ischemia time, number of previous transplants, panel reactive antibodies, HLA-mismatches, induction therapies, maintenance immunotherapy, and donor factors (donor type, donor age). RTxRs were divided based on induction therapy into r-ATG and IL-2RA. Instrumental variable regression models were used to assess the effect of induction therapy on acute rejection episodes at 12 months post-transplant, serum creatinine levels at 12 months post-transplant, and graft survival. Type of induction therapy was instrumented for the transplant center to reduce the center effect on the choice of the induction therapy. The regression models were adjusted for the collected recipient, donor, and transplant factors.

Results: 788 patients received Basiliximab while 1727 patients received Thymoglobulin induction. There were no significant differences between Basiliximab versus Thymoglobulin induction in acute rejection episodes at one-year post-transplant (coefficient=-0.229, P value=0.106, 95% Confidence interval:-0.5086 to 0.049), serum creatinine levels at one-year post-transplant (coefficient=-0.024, P value=0.128, 95% Confidence interval:-0.355 to 0.006) or overall graft survival (coefficient=-0.008, P value=0.801, 95% CI:-0.001 - 0.001).

Conclusions: The study showed no significant difference in acute rejection episodes or graft survival when using Thymoglobulin or Basiliximab in 2DR HLA mismatched living donor renal transplant recipients in the current tacrolimus-based maintenance immunosuppression era. Therefore, Basiliximab is a safe induction therapy in this group of patients.

PO2128
Outcomes of Early and Late Calcium Oxalate Deposition Following Kidney Transplantation
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Background: Calcium oxalate deposition (CaOx) can result in progressive native kidney disease. The pathophysiology of hyperoxaluria in kidney transplant (KT) differs, especially early after surgery when the allograft encounters high levels. It is not clear whether CaOx in a kidney allograft portends worse outcomes. Determining its clinical relevance will influence the need for aggressive dietary or medication-based interventions.

Methods: All KT recipients at our center with CaOx on kidney allograft biopsy were categorized into two cohorts: delayed graft function (DGF; n=13) and late graft dysfunction (n=25). Up to 5 controls were selected per DGF case from event density sampling matched for organ type (kidney vs. simultaneous pancreas-kidney), prior transplants, and history of prolonged DGF prompting a biopsy (n=46). Controls for ‘late’ cases were matched for organ type, prior transplants, and living vs. deceased donor (n=125). Variables found to be statistically significantly associated with case status in bivariate analysis (p<0.10) were included in multivariate Cox regression analyses of allograft outcomes.

Results: DGF cases were more likely to have had gastric bypass surgery (7.7% vs. 0%, p=0.06) and less likely to have a history of rejection (7.7% vs. 37.0%, p=0.06) than controls. CaOx during DGF was not associated with increased risk of graft failure after adjustment (HR 1.1, p=0.87; Figure 1). ‘Late’ CaOx cases diagnosed median of 56.7 months (IQR: 9.8-108.9 months) after transplant were older at time of transplant (53.9 vs. 48.4 years, p=0.04) and less likely to be male (36% vs 61%, p=0.03) than controls. ‘Late’ CaOx was associated with a higher risk of allograft failure after adjustment (HR 3.2, p<0.001; Figure 2).

Conclusions: CaOx in kidney allograft during DGF may be a consequence of high circulating oxalate levels and was not associated with worse KOttoumes. ‘Late’ CaOx, likely related to increased intestinal oxalate absorption, a phenotype similar to secondary hyperoxaluria in native kidneys, was associated with increased risk of allograft failure.
PO2130

Chronic Active Antibody-Mediated Rejection: Response Rates to Treatment and Predictors of Graft Survival

Fahad Aziz, Sandesh Parajuli, Neetika Garg, Maha A. Mohanned, Didier A. Mandelbrot, Arjang Djamali. University of Wisconsin System, Madison, WI.

Background: There is limited information on response rates to Rx and predictors of graft survival following chronic active antibody mediated rejection (cABMR).

Methods: We reviewed changes in kidney function, DSA, and histology in 3-month surveillance biopsies after initial therapy with pulse steroids/IVIG or rituximab in kidney transplant recipients with cABMR between 01/2017 and 08/2020. Rx response was defined as ≥30% improvement in eGFR (i.e., ≤30% eGFR decline) following biopsy. Response was defined as a return to baseline eGFR at 3M after initial biopsy was the best predictor of graft survival in patients with cABMR. Short-term histological and immunological response to treatment were not independently associated with graft survival.

Results: The study included 82 patients. 50% received rituximab. Mean time from Tx to cABMR was 10 years. Mean eGFR was 61 mg/dL, and mean eGFR decrease was 49 mg/dL. Response rates to rituximab and pulse steroids/IVIG were 60% and 30%, respectively. On univariate analysis, rituximab use (HR=0.13, p=0.0001, 95%CI 0.05 to 0.34) and a response in eGFR (HR=0.03, p=0.001, 95% CI 0.004 to 0.26), UPC (HR=0.38, p=0.01, 95%CI 0.18 to 0.82), and DSA (HR=0.11, p=0.004, 95%CI 0.02 to 0.49) were associated with improved death-censored graft survival. Multivariate analysis only retained rituximab response (HR=0.12, p=0.01, 95%CI 0.02 to 0.64).

Conclusions: Our study suggests that a return to baseline eGFR at 3M after initial biopsy is the best predictor of graft survival in patients with cABMR. Short-term histological and immunological response to treatment were not independently associated with graft survival.

Response Rate at Surveillance Biopsy

<table>
<thead>
<tr>
<th>Response</th>
<th>Steroid/IVIG</th>
<th>Steroid/IVIG/Rituximab</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>14 (42.4%)</td>
<td>24 (67.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>UPC</td>
<td>24 (61.5%)</td>
<td>25 (62%)</td>
<td>0.11</td>
</tr>
<tr>
<td>DSA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.007</td>
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</tbody>
</table>

Figure. Rituximab was Associated with Improved Graft Survival

PO2131

Outcomes of Acute and Chronic Antibody-Mediated Allograft Rejection in Kidney Transplant Recipients

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Background: The optimal treatment regimen for antibody-mediated rejection (AMR) in kidney transplant recipients (KTRs) has yet to be established. The purpose of the study was to evaluate the outcomes of KTRs with acute and chronic AMR managed with different treatment regimens. Method: We conducted a retrospective cohort study of all KTRs with biopsy-proven acute or chronic AMR between January 2017 and September 2020 at a single center. The primary outcome was allograft loss at last follow up. Secondary outcomes included differences in allograft survival between treatment regimens, and changes in estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UCPR) at last follow up.

Results: 53 KTRs with AMR were included in the study. Mean age was 51 years, 50% were female and the most common cause of end-stage kidney disease was glomerular disease. 57% received living donor transplants, median number of human leukocyte antigen ABDR mismatches was 4, and 38% had pre-transplant donor-specific antibodies. For induction immunosuppression, 61% received anti-thymocyte globulin, 35% received basiliximab and 4% received alemtuzumab. 35% had acute AMR and 65% had chronic-active AMR. Mean eGFR at biopsy, median (IQR) eGFR was 32 (22-42) ml/min/1.73 m² and UCPR was 1.1 (0.4-2.5) g/g. For treatment, 72% received pulse steroids, 64% received intravenous immunoglobulin, 51% received plasma exchange (PLEX) and 43% received bortezomib. At a median follow up of 23 months, patient survival was 94% and death-censored allograft survival was 74%. Median (IQR) eGFR was 27 (11-43) ml/min/1.73 m² and UCPR was 0.48 (0.17-0.97) g/g. There was no difference in the risk of allograft loss in patients who received PLEX compared to those who did not (RR=0.97, 95% CI: 0.4-2.4) and in those who received bortezomib compared to those who did not (RR=0.8, 95% CI: 0.3-2.0). The risk of allograft loss was higher in KTRs with UCPR>3 g/g at AMR diagnosis compared to those with <3 g/g (RR 4.3, 95% CI: 1.6-11.6).

Conclusions: Higher proteinuria at AMR diagnosis is associated with a higher risk of allograft loss. Use of PLEX or bortezomib was not associated with lower risk of allograft failure in KTRs with AMR. Novel treatment regimens are needed to improve the outcomes of KTRs with acute and chronic AMR.

Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Healthy Controls</th>
<th>Chronic AMR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/dL)</td>
<td>61.5±24.3</td>
<td>50.7±28.7</td>
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<tr>
<td>UCPR (g/g)</td>
<td>0.3±0.2</td>
<td>3.0±3.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD.

Figure 1
PO2133
Monoclonal Gammapathy in Kidney Transplanted Patients: Novel Insights into Long-Term Outcomes

Marie-Sophie Anglicheau,1,2 Juliette Gueguen,3 Stephanie Vicca,3 Olivier Aubert,1 Bertrand Arnulf,1 Dayni Anglicheau,1 Frank Bridoux,2 Camille Cohen,3 Hospital universitaire Necker-Enfants malades, Paris, France; 4Centre Hospitalier Universitaire de Poitiers, Poitiers, France; 5Hôpital Saint-Louis, Paris, France.

Background: Monoclonal gammapathy (MG) is a frequent condition affecting 0.5 to 6% of general population. Little is known about the prevalence of MG and its consequences on long-term outcomes in the setting of kidney transplantation (KT).

Methods: We conducted a monocentric retrospective cohort study based on 2272 patients who underwent a KT from January 2007 to June 2019 at Necker Hospital Paris, France. A systematic extraction of serum protein electrophoresis (SPEP) results performed during this period was used to distinguish patients with MG at the time of KT (MGKT) and patients who developed de novo MG (DVMG) after KT. Serum free light chain (FLC) were retrospectively measured on stored frozen sera from MGKT patients, taken at the day of KT.

Results: We identified 66 patients with MGKT and 79 with DVMG. Patient’s characteristics are summarized in Table 1. Eleven (6%) patients developed a hematological disorder, i.e. post transplantation lymphoid disorder (n=6) and multiple myeloma (n=5), without difference between groups. Infectious complications were similarly frequent, regarding viral (n=68, 47%), bacterial (n=96, 66%) and fungal infections (n=12, 14%). Strikingly, median overall survival was significantly lower in MGKT patients compared to DVMG patients (78 months vs not reached, respectively, p=0.005). The five MGKT patients with an abnormal sFLC ratio (<0.3 or >3.3) at the time of KT tended to have lower OS compared to those with normal sFLC ratio (p= 0.07), suggesting that abnormal FLC ratio might represent a risk factor for early death in KT recipients. Death censored graft survival was not different between groups.

Conclusions: By analyzing the most important cohort of KT patients with MG reported to date, we found that MGKT affects overall survival and that sFLC measurement at the time of KT may refine risk stratification. Measurement of sFLC and SPE should be incorporated to the pre-transplant evaluation workup.

Funding: Government Support - Non-U.S.

General characteristics

Table 1: Annual change in eGFR

Table 2: Outcomes by induction therapy between 2009-2019

PO2134
Renal Outcome and Infectious Complications Associated with Induction Regimens for Kidney Transplantation Among Children: A NAPRTCS and PHIS Collaborative Study

Daniella Levy Frez,1,2 Helen Pizzo,4 Nancy M. Rodig,3 Troy Richardson,3 Michael J. Somers,3 1The Children’s Hospital of Philadelphia, Philadelphia, PA; 2Schneider Children’s Medical Center of Israel, Petah Tikva, Israel; 3Boston Children’s Hospital, Boston, MA; 4Cedars-Sinai Medical Center, Los Angeles, CA; 5Children’s Hospital Association, Overland Park, KS.

Background: Few studies compare induction agents in pediatric kidney transplants (KTx), and induction is often guided by local practice more so than specific outcome data. We evaluated how different agents affected outcomes in children enrolled in both the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry and the Pediatric Health Information System (PHIS).

Methods: Retrospective study of merged data from NAPRTCS and PHIS between 1998-2019. Participants grouped by induction agent: no induction, IL2 RB only, cATG/ALG, almtuzumab. Estimated GFR (eGFR) was calculated with adjustments for age, diagnosis, repeat KTx status, delayed graft function, and rejection. Subgroup analysis evaluated rejection rates and infectious complications between 2009-2019. Outcomes were compared using chi-square or Kruskal-Wallis tests.

Results: 2410 KTx recipients with data in both datasets were identified. 340 subjects were compared using chi-square or Kruskal-Wallis tests.

Conclusions: Longitudinal decline in eGFR was similar across all induction agents, though decline with ATG/ALG was lowest. Although rejection and BK viremia was lower with almtuzumab, there was no difference with EBV or CMV infection or post-KTx malignancy.

Funding: Private Foundation Support

PO2135
Bacteremia in Kidney Transplant Recipients with Septic Arthritis Is Perilous

James D. Alastatt, Margaret R. Jorgenson, Christopher Saddler, Sandesh Parajuli, Nazlika Garg, Maha A. Mohamed, Didier A. Mandelbrot, Arjang Djamali, Fahad Aziz, University of Wisconsin-Madison, Madison, WI.

Background: Features and clinical sequelae of septic arthritis in the general population have been described; however, the epidemiology and outcomes of septic arthritis in kidney transplant recipients (KTRs) is limited, and the potential impact on graft function has not been reported.

Methods: A single-center, retrospective, observational cohort study including patients with a history of kidney transplant and subsequent septic arthritis between 1/1997-12/2017 was performed.

Results: During the 20-year study period, 6184 patients received kidney and pancreas transplants, of these 65 (1%) patients had documented diagnosis of septic arthritis. 51 patients had kidney alone transplants and 14 had simultaneous kidney and pancreas transplants. The mean age at the time of transplant was 50 ± 10.4 years. The mean time from the transplant to the septic arthritis diagnosis was 6.6 ± 6 years. The most commonly affected joint was the knee (38%), followed by the shoulder (11%) and hip (9%). Joint with hardware accounted for 14 (21.5%) cases. Staphylococcus species were the most commonly isolated bacteria (52%) followed by gram-negative rods (14%). Only two patients had fungus isolated from joint aspiration (one histoplasm and one aspergillus). Antimicrobials were used in all of the patients. The majority of patients were treated with either joint aspiration (39%) or I&D (39%). The need for curative amputation was uncommon (4%). When evaluating subsequent graft function, the mean eGFR declined 12 ± 8 ml/min/1.73 m2 at one year after diagnosis. The presence of bacteremia at time of diagnosis was associated with significant worse joint (HR 5.37, p<0.01, 95%CI 1.57 to 18.41) and graft outcomes (HR 5.37, p=0.004, 95%CI 1.53 to 9.55). By last follow up, 21 patients lost their allografts and 28 patients died with functional kidney graft.

Conclusions: Septic arthritis is an uncommon complication in KTRs. When seen, it typically occurs >1 year after transplant with similar pathogens and management as in the general population. However, it appears to be associated with negative graft effects. A high index of suspicion, timely diagnosis, and appropriate management are needed to ensure optimal outcomes for septic arthritis in KTRs.

PO2136
Clinical Significance of Vitamin D on Preexisting and Post-Transplant Diabetes Mellitus in Kidney Transplantation: Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT)

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Background: Kidney transplant recipients (KTRs) with preexisting DM or post-transplant diabetes mellitus (PTDM) have poor clinical outcomes. An association between vitamin D and diabetes mellitus (DM) has been reported, but there are few reports for impact of vitamin D on preexisting DM and PTDM.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Table 1: Annual change in eGFR

Table 2: Outcomes by induction therapy between 2009-2019

Table 3: Results of Cox regression analysis
Methods: A total of 995 KTRs were enrolled in KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) between July 2012 and August 2016. KTRs were categorized into 3 groups: nondiabetic, preexisting DM and PTDM. Vitamin D status at KT was defined to deficiency (<10 ng/ml), insufficiency (10-30 ng/ml), and normal (≥30 ng/ml). This study aims to investigate clinical significance of vitamin D based on diabetic status in KTRs. Results: Nondiabetic group was 643 (64.6%), preexisting DM group, 267 (26.8%), and PTDM group, 85 (8.5%). In all groups, vitamin D levels gradually increased after KT, then showed equilibrium at 2 years, and decreased after 4 years, but there was no significant difference of vitamin D levels. The proportion of vitamin D deficiency at KT was the highest in preexisting DM group compared with other groups, but there was no significant difference of that since 1 year after KT. There were no significant differences of immunologic findings among the rate. The rate of cardiovascular event was significantly higher in preexisting DM group compared with other groups (P=0.001). Death-censored graft survival rate was significantly lower in preexisting DM compared with other groups (P=0.049), but there was no significant difference according to vitamin D status. Death-censored graft survival rate in KTRs with preexisting DM and vitamin D deficiency was the lowest, and it showed the significant synergistic effect on the allograft outcome (P=0.022). In the multivariate analysis, older age was an independent risk factors for allograft failure (HR 1.045, 95% C.I. 1.005-1.087, P=0.026). Patient survival rate was significantly lower in preexisting DM group compared with other groups (P=0.008).

Conclusions: The prognostic of KTRs with preexisting DM and vitamin D deficiency was the worst comparing nondiabetic and PTDM groups. Therefore, careful monitoring after KT of candidates with pre-transplant DM and vitamin D deficiency is required.

PO2137
Preeclampsia and Kidney Transplant: Offspring and Mother Outcomes in a Single-Center Cohort in the West of Mexico

Background: Pregnancy in a kidney transplant recipient (KTR) is possible and safe after a 1-2 year post transplantation, stable serum creatinine (<1.5 mg/dL), controlled or no hypertension, proteinuria in 24 hours <500 mg and stable immunosuppressive levels. Preeclampsia is a common complication in KTR pregnant women associated to worse maternal and offspring outcomes, there is scarce available information this topic in a KTR in Latin America.

Methods: Retrospective cohort study from October 2018 to April 2021 included 18 patients >18 years who got pregnant after KT. Serum creatinine (Scr), proteinuria before, during pregnancy and after delivery, the presence of hypertension before pregnancy, episodes of kidney graft rejections, immunosuppressant therapy, and preeclampsia were recorded from medical chart, and compared it to the offspring’s gestational age, weight, APGAR score, NICU requirement and NICU stay.

Results: The frequency of preeclampsia was 33%, none of them were diagnosed with hypertension before pregnancy. Three women died after delivering (no obstetric associated), 1 lost graft function (in PD). Scr was higher during pregnancy and after delivery, offspring’s gestational age was lower, offspring’s weight was considerably lower, as well as APGAR score in women with preeclampsia, all NICU requirement were in children whose mother had preeclampsia and they had a NICU media stay of 19 days. In a logistic regression analysis, preeclampsia is a risk factor to a lower APGAR SCORE (p=0.001), requirement of NICU (p=0.001) and NICU stay. Other results are shown in the table.

Conclusions: Age, time between KT and pregnancy, gestational age, hypertension, serum creatinine, cesarean delivery was not different among preeclampsia, compared to the control group. Children from preeclamptic women tend to have lower weight and had lower apgar score and higher NICU requirement.

Funding: Government Support - Non-U.S.
correlated depression (Rho=0.61, p<0.001) and physical functioning (Rho=0.72, p<0.001). The Self and Other” subscale was moderately correlated with depression (Rho=0.56, p<0.001). SD16 scores were higher for patients on dialysis vs KT (median[interquartile range – IQR] 7[3,13] vs 3[1,8],p<0.001). “Everyday Living” scores were higher in patients with Charlson Comorbidity Index of ≥2 (3[0,6] vs 1[0,3],p<0.001). “Money Matters” scores were higher in individuals facing high vs material deprivation (1[0,4] vs 0[0,3], p<0.008). “Self and Other” scores were higher in participants that are uncomfortable or reluctant in relationships vs those that find it easy (3[1,7] vs 1[0,3],p<0.002).

Conclusions: These results suggest that the SD-16 and its subscales have good reliability and structural validity. Further research is required to explore the potential clinical benefits of using the SD16 in patients with kidney failure.

PO2140
Symptom Management Preferences of Kidney Transplant Recipients and Caregivers

Background: Kidney transplant (KT) recipients frequently experience physical, emotional, and social challenges. These are often undermanaged and can lead to impaired quality of life. Better understanding of the perspectives of KT recipients and their caregivers about their symptom experiences and management needs will improve post-transplant care for KT recipients.

Methods: As part of a larger study aimed at developing a patient-centered electronic assessment toolkit, adult (≥18 years) KT recipients and caregivers of KT recipients were recruited for this study via flyers. Patients not fluent in English or cognitively impaired were excluded. Qualitative description was used to explore and understand participants’ post-transplant experiences and preferences. A semi-structured interview guide with open-ended questions was used to facilitate in-depth, individual interviews. Interviews were audio recorded and transcribed verbatim. Transcripts were analyzed via content analysis using deductive and inductive coding strategies. Codes and categories were developed and refined by the research team.

Results: Seven KT recipients and one caregiver (age: 52-76 years, 8-20 years post-transplant, 5/8 male) participated. Participants identified significant challenges in physical (e.g. fatigue, sleep disturbances, weight or mobility issues); emotional (e.g. depression, anxiety); and social (e.g. financial challenges, self-care, social roles) domains. Participants considered fatigue as the most troublesome symptom. Furthermore, participants described the clustering of their post-transplant symptoms across domains. For example, fatigue and sleep disturbances were experienced and with depression and the inability to perform self-care activities and maintain relationships. Participants also expressed that their post-transplant care centered on physical symptoms with little exploration and support of psychological and social issues. Finally, participants emphasized that a care plan integrating all aspects of health is needed to adequately support their needs.

Conclusions: This analysis identified a range of patient-valued, physical, emotional, and social concerns, with fatigue being the most troublesome symptom. These findings will inform the development of future interventions to improve patient-centered post-transplant care.

PO2141
Airflow Limitation, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients
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Background: Many kidney transplant recipients (KTR) suffer from fatigue and poor health-related quality of life (HRQoL). Airflow limitation may be an underappreciated comorbidity among KTR, which could contribute to fatigue and poor HRQoL in this population. In this study, we compared the prevalence of airflow limitation between KTR and healthy controls (HC), and investigated associations of airflow limitation with fatigue and HRQoL in KTR.

Methods: Data from the ongoing TransplantLines Biobank and Cohort Study (NCT03232841) were used. Airflow limitation was defined as forced expiratory volume in one second (FEV1) <5th percentile of the general population. Fatigue and HRQoL were assessed using CIS20R and SF-36 questionnaires.

Results: A total of 539 KTR (58% male, mean age 56 ± 13 years) and 244 HC (45% male, mean age 57 ± 10 years) were included. Prevalence of airflow limitation was higher in KTR than in HC (133 (25%) vs 25 (10%), p<0.001). Airflow limitation was independently associated with higher risk of severe fatigue (OR 2.53, 95%CI 1.41 to 4.55, p=0.002) and poor HRQoL (physical component score (PCS): st. β = -0.12, 95%CI -0.20 to -0.03, p<0.005 and mental component score (MCS): st. β = -0.10, 95%CI -0.19 to -0.01, p=0.034) in KTR. Fatigue mediated the association of airflow limitation with PCS and MCS for 76.2% and 99.6%, respectively (Figure 1).

Conclusions: Airflow limitation is common among KTR. Its occurrence more than doubles the risk of severe fatigue, and is associated with poor HRQoL. Mediation analyses suggest that airflow limitation causes fatigue which in turn decreases HRQoL. Since airflow limitation can be improved by treatment and training, it may be a promising therapeutic target to reduce fatigue, and consequently to improve HRQoL among KTR.

PO2142
Outcomes of Liver Transplant Recipients Who Developed AKI Before Liver Transplant
Pyavadee Hongkralai,1,2 Suphamai Bunnapradist.1 1University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 2Bhumibol Adulyadej Hospital, Bangkok, Thailand.

Background: Multiple factors including level of kidney function, patient comorbidities and functional status may influence the decision whether to simultaneous liver-kidney (SLK) transplant or waiting for kidney function recovery in end stage liver disease. Consequence of waiting for subsequent kidney transplant (KT) those without kidney recovery is unknown.

Methods: The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data of patients who were initially listed for liver transplant (LT) alone who also developed acute kidney injury (AKI) requiring dialysis within 60 days before LT and subsequently listed for KT during year 2000 – 2018 were included. Kidney function recovery defined as discontinuing dialysis >1 year. Our cohort therefore included (1) SLK, (2) listed for subsequent KT within one-year after LT and (3) listed for subsequent KT after recovery.

Results: A total of 7,653 liver recipients received dialysis within 60 days before LT. There were 110 patients receiving SLK and 445 patients listing for subsequent KT within one-year. Seven thousand two hundred and ninety-eight patients had kidney function recovery and 301 (3.8%) patients were listed for subsequent KT after dialysis free >1 year. One-year patient survival rates were 78.1% (95%CI 69.2 – 84.8) and 86.0% (82.4 – 88.9) among receiving SLK and listing for subsequent KT within one-year group, respectively. Ten-year patient survival rates were 45.5% (35.2 – 55.0) and 49.2% (42.8 – 55.3), respectively. Patients who survive and had dialysis-free more than one year had the best ten-year survival which were 62.9% (55.8 – 69.1).

Conclusions: Only 7.1% of liver recipients who developed AKI requiring dialysis within 60 days before LT did not have kidney recovery and remain on dialysis. These patients who received SLK had lower one-year patient survival but comparable ten-year patient survival compared to patients who listed for subsequent KT within one-year after LT.

PO2143
Clinical Outcome After Combined Liver and Kidney Transplantation in Children in Europe: A CERTAIN Registry Analysis
Florian Brinkert,1 Katja Goroniti,1 Justine Bacchetta,4 Anja K. Büscher,2 Luca Dello Strologo,1 Deirdre Kelly,2 Markus J. Kemper,2 Lars Pape,4 Marek Szymczak,4 Burkhard Toenhoff,4 Jun Oh,3 Universitatsklinikum Hamburg Eppendorf Klinik für Kinder- und Jugendmedizin, Hamburg, Germany; 2Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham, United Kingdom; 3Universitatsklinikum Essen Klinik für Kinderheilkunde II, Essen, Germany; 4Hospices Civils de Lyon, Lyon, France; 5Asklepios Kliniken Hamburg GmbH Asklepios Klinik Nord Standort Heidberg, Hamburg, Germany; 6Institut Pomnik -Centrum Zdrowia Dziecka, Warszawa, Poland; 7Ospedale Pediatrico Bambino Gesù, Roma, Italy; 8Universitatsklinikum Heidelberg Zentrum für Kinder- und Jugendmedizin, Heidelberg, Germany.

Background: Combined liver and kidney transplantation (CLKT) in children is still a challenging procedure and therefore performed only in specialized centers. Outcome of these patients is mostly published as single center reports. To gain more insights in outcome and specific challenges of this rare disease group we aimed for an European registry analysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We conducted a multi-center, retrospective, cohort study using data of the Consortium of European Pediatric Renal Transplant Initiative (CERTAIN) registry (www.certain-registry.eu). The CERTAIN registry provides transplantation-related data of kidney allograft recipients ≥21 years at transplantation of 75 pediatric renal transplant centers in Europe. For this specific study we established an additional dataset for liver allograft recipients which includes essential liver transplantation-related data. The survival curves were assessed with the Kaplan-Meier method and compared with the log-rank test. The statistical analyses were performed with SPSS, Version 27.

Results: In the study we analyzed 159 patients from 13 transplantation centers. The median follow-up time was 3.9 years (range, 5 days-17 years). Patient survival was good with 9 deaths reported. This led to an overall patient survival of 94% with no difference between PH1 and ARPKD. The kidney and liver graft survival rates were 92.5% and 91.1%, respectively. Long-term eGFR calculations showed stable renal function until 9 years of follow-up. Thereafter, kidney function slowly deteriorates. Liver function tests were stable over the whole study period.

Conclusions: CERTAIN registry data showed that CLKT lead to an excellent patient and graft survival with a similarity between PH1 and ARPKD patients. In addition, patient survival after CLKT is comparable to isolated liver or kidney transplantation. The retrospective study design may have led to a reporting bias.

PO2144
Renal Outcomes After Liver Transplantation in the MELD-Na Score Era in Patients with Pre-Transplant Renal Impairment
Roger Lin, Nevin Varghese, Sung Choi, Abdulreza Harritan, Wen Y. Xie, Daniel G. Maluf, Matthew R. Weir. University of Maryland School of Medicine, Baltimore, MD.

Background: Post-liver transplant (LT) renal insufficiency is an established predictor of morbidity and mortality for liver transplant recipients. Current reports on renal outcomes after liver transplantation (LT) have exclusively focused on patients from the MELD era. There is little information on the progression of kidney disease since the implementation of the MELD-Na scoring system. We sought to characterize the prevalence of kidney disease after LT and its risk factors during the MELD-Na era.

Methods: This is a retrospective cohort study of 107 adult, single-organ, primary liver transplant patients performed at the University of Maryland Medical Center between January 2016 and January 2017, after implementation of the MELD-Na scoring system. We determined the pre-transplant chronic kidney disease (CKD) status (defined as eGFR ≤60mL/min per 1.73 m² or dependence on renal replacement therapy) by using the CKD-EPI Creatinine equation, available lab values, and the renal replacement therapy (RRT) status within the 90 days prior to transplant. The primary outcome was persistent CKD or mortality at 12 months. Recipients of MELD-Na exception scores as well as Status 1 liver transplants were excluded.

Results: The mean patient age was 54.2 ± 11.7 years, 74 male, 85 Caucasian, 30 had diabetes, 55 were hypertensive, and 27 had HCV. 32 patients had pre-LT renal insufficiency and 25 patients were on RRT at the time of LT. The overall 1-year mortality rate post-LT was 11.2%. 36 patients had CKD at 12 months. Among the patients with pre-LT renal insufficiency, 13 demonstrated improved renal function, 13 remained with CKD, 2 ended up on long-term RRT, and 4 died by 12 months. Renal insufficiency equivalent to CKD stage 4 prior to LT (OR 8.75, CI 9.07-78.7, p = 0.053) and RRT at time of LT (OR 3.6, CI 4.2-9.55, P = 0.007) were independently associated with increased risk of renal death or CKD at 12 months. Other variables including age, sex, HCV, DM, HTN, CKD Stage 3, MELD-Na score, BMI, and organ rejection were not predictive of the outcome.

Conclusions: Our study in the MELD-Na era patients suggests that 40% of the patients had pre-transplant renal dysfunction pre-LT which deteriorated to function by 12 months post-LT. RRT at the time of LT, and moderate to severe renal impairment prior to LT are risk factors for recipient mortality or persistent CKD at 1 year post-LT.

PO2145
Gender Disparities in Access to Simultaneous Liver-Kidney Transplantation in the Pre- vs. Post- Allocation Policy Eras
Giselle Peschard,1 Mei Wang,1 Yazen Al-Hosni,1 Krista L. Lentine,2 Su-Hsin Chang,1 Tarek Alhamad.1 1Washington University in St Louis, St Louis, MO, 2Saint Louis University School of Medicine, Saint Louis, MO.

Background: Gender differences in receiving simultaneous liver-kidney transplant (SLKT) is not well-understood. We recently found that women are disadvantaged in access to organ transplantation. For this specific study we established an additional dataset for liver allograft recipients which includes essential liver transplantation-related data. The survival curves were assessed with the Kaplan-Meier method and compared with the log-rank test. The statistical analyses were performed with SPSS, Version 27.

Methods: We conducted a multi-center, retrospective, cohort study using data of the Consortium of European Pediatric Renal Transplant Initiative (CERTAIN) registry (www.certain-registry.eu). The CERTAIN registry provides transplantation-related data of kidney allograft recipients ≥21 years at transplantation of 75 pediatric renal transplant centers in Europe. For this specific study we established an additional dataset for liver allograft recipients which includes essential liver transplantation-related data. The survival curves were assessed with the Kaplan-Meier method and compared with the log-rank test. The statistical analyses were performed with SPSS, Version 27.

Results: In the study we analyzed 159 patients from 13 transplantation centers. The median follow-up time was 3.9 years (range, 5 days-17 years). Patient survival was good with 9 deaths reported. This led to an overall patient survival of 94% with no difference between PH1 and ARPKD. The kidney and liver graft survival rates were 92.5% and 91.1%, respectively. Long-term eGFR calculations showed stable renal function until 9 years of follow-up. Thereafter, kidney function slowly deteriorates. Liver function tests were stable over the whole study period.

Conclusions: CERTAIN registry data showed that CLKT lead to an excellent patient and graft survival with a similarity between PH1 and ARPKD patients. In addition, patient survival after CLKT is comparable to isolated liver or kidney transplantation. The retrospective study design may have led to a reporting bias.

PO2146
Gender-Based Disparities in Access and Survival Outcomes of Simultaneous Liver-Kidney Transplant Among Liver Transplant Candidates with Renal Dysfunction in the United States
Giselle Peschard,1 Mei Wang,1 Yazen Al-Hosni,1 Krista L. Lentine,2 Su-Hsin Chang,1 Tarek Alhamad.1 1Washington University in St Louis, St Louis, MO, 2Saint Louis University School of Medicine, Saint Louis, MO.

Background: The frequency of simultaneous liver-kidney transplantation (SLKT) has risen since the implementation of the Model for End-stage Liver Disease (MELD)-liver allocation system. Gender disparities in access to SLKT and outcomes post-transplantation are not well described. We examined these gender-based disparities in the MELD era.

Methods: We included a retrospective cohort of patients wait-listed for liver transplant (LT) between 2002-2017 with renal dysfunction (RD). Multilevel time-to-competing-events regression adjusting for center effect was used to examine the likelihood of receiving SLKT. Inverse probability of treatment weighted (IPTW) survival analyses were used to analyze posttransplant mortality outcomes. Sensitivity Analysis (SA) performed using 2 alternative definitions of RD for LT candidates: SA(1), either received dialysis or having creatinine ≥2.0 mg/dL at listing for LT, and SA(2), either received dialysis or having eGFR<35 mL/min/1.73 m2 at listing for LT.

Results: Among candidates not listed for SLKT at the time of listing for LT, females had a 50% lower likelihood of receiving SLKT compared to males (Figure 1). Females continued to have reduced access despite being listed for SLKT. Once transplanted, we found no statistically significant difference in post-transplant survival by sex for SLKT or LT alone recipients (Figure 2).

Conclusions: Prior to the implementation of the SLKT allocation policy, gender disparities were found in access to SLKT but not in post-transplant survival. A tighter gender difference in access to SLKT was found amongst patients listed for SLKT compared to those not listed simultaneously.

Figure 1: Multivariable-adjusted hazard ratios for receiving SLKT pre- and post-SLKT allocation policy by gender.

Figure 3: Multivariable-adjusted hazard ratios for receiving SLKT 2002-2017.*
PO2147

Development Following Paediatric Kidney Transplantation

Lars Pape, Jenny Pruelle. Universität Duisburg-Essen, Essen, Germany.

Background: This study aims to assess quality of life, mental health, motor development, executive functioning and medication adherence in paediatric patients following kidney transplantation.

Methods: In a cross-sectional study we used standardised tools (FABEL, KINDL, PedsQL, CBCL, M-ABC, WISC-V, BAASSIS) to assess the relevant parameters and analyse them against the background of selected medical data.

Results: We included 53 kidney transplanted children aged 0-18 (♂52; ♀1). Parents reported increased financial burden and fear of the future. Half of the patients showed some symptoms of mental distress. 13/40 (32.5%) patients fulfilled DSM-criteria for mental health problems. Most frequent symptoms linked to depression and anxiety. Participants who started renal replacement therapy in their first three years of life mainly expressed symptoms of the externalising spectrum. Motor-development could be assessed in 47 patients. Developmental deficits could manifestly be observed in the field of fine motor skills and dexterity as well as body-balance. In total 11/47 (23.4%) patients had fine-motor-skills below the 2nd percentile, 14/47 (29.9%) had deficits in body-balance scoring below the 2nd percentile.

Conclusions: Even after successful transplantation chronic kidney disease seams to impact on the overall health and development of the affected child. While nowadays allograft survival is considered to be acceptable, it is time to shift focus on quality of survival and non-renal consequences of a renal disease. Besides further research clinical programs are needed to offer tailored assessments and support.

PO2148

Long-Term Outcomes of Kidney Transplantation in a Disadvantaged Population in Mexico

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Background: Access to kidney transplantation in Mexico was limited to patients with social security. Since 2010 at the Dr. Eduardo Liceaga General Hospital of Mexico, a kidney transplant program was established for patients with terminal chronic kidney disease living in extreme poverty or without social security. We aim to analyze the long-term outcomes of kidney transplantation in a disadvantaged population.

Methods: During the study period, 345 transplants were performed. The median age was 31.5 ± 11.58 years, 58.6% were men and 74% of the transplants were from living donors. Ninety patients (26%) had social security (With SS) and 255 patients (74%) were in disadvantaged conditions from 2010 to 2020 were analyzed. The significant predictors of total complications were 0.1% ± 0.05 and 0.19 ± 0.08, respectively. A higher frequency of acute rejection and alloimmune-mediated rejection was observed in patients without social security (Without SS) at the time of transplantation were analyzed. The median time from KT to IBD diagnosis was 6 years (range, 2–12). Allograft function did not worsen after IBD in any recipients. The initial presentation was bloody stool in 5 recipients and mild diarrhea in 1. In the recipient with CD, severe and continuous abdominal pain, and bloody stool with moderately elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were present (3.33 mg/dL and 71 mm/h, respectively). In recipients with UC, bloody stool or mild diarrhea without abdominal pain, and mild to moderate inflammation markers such as median CRP [0.28 mg/dL (range: 0.07–38 mg/dL)] and median ESR [26.5 (5–91.8 mm/h)] were present. Three recipients with UC had HLA B52, DR2, or DR5, which are known to associate with UC. All recipients received a triple maintenance IM for KT including tacrolimus and steroids. Regarding treatment for de novo IBD, infliximab for the recipient with CD and 5-aminosalicylate for recipients with UC were used as a primary treatment. One recipient with UC affected the whole colon was resistant to prednisolone, infliximab, and vedolizumab. He eventually underwent total colectomy at 1-year after diagnosis. The others achieved the remission of IBD after initial therapy.

Conclusions: De novo IBD should be a differential diagnosis of bloody stool after KT in spite of low or only mildly elevated inflammation markers. De novo IBD can present even without bloody stool.

PO2150

Renal Transplant Biopsy Outcomes: A Nephrology and Radiology Standpoint in an Academic Center

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Background: Renal transplant biopsies are the gold standard for evaluating allograft dysfunction. Studies comparing biopsy safety outcomes between transplant nephrologist and interventional radiologist are lacking. We describe our academic center experience and compare their risk factors.

Methods: This is a retrospective study of patients who underwent percutaneous ultrasound-guided renal transplant biopsy (US-RTB) at a single center between January 2013 to August 2016. This cohort was stratified into two groups according to the team that performed the biopsy: interventional radiology(IR,n=448) and transplant nephrology(TN,n=231). The predictors of post-biopsy complications were assessed by multivariate logistic regression.

Results: A total of 678 US-RTB were performed in 573 patients. There was no significant difference in the rate of total complications, blood transfusion, or periphereal hematoma between the IR and TN groups. The regression analysis showed that the team that performed the biopsy was not a significant predictor for total complications, blood transfusion, or periphereal hematoma. The significant predictors of post-biopsy complications were 0.1% ± 0.05.21. There were significant differences in immunosuppressive induction and maintenance schedules between groups. Patients Without SS more frequently received only steroids as induction therapy and cyclosporine as maintenance therapy (p=0.05). A higher frequency of acute rejection and chronic rejection was observed in patients Without SS (p≤0.05). No differences were observed in metabolic, cardiovascular or infectious complications after transplantation. With an average follow-up of 6.23 ± years, not difference was identified in graft survival (With SS: 84.7% vs Without SS: 85.9%, p=0.222), nor in patient survival (88.5% versus 84.3%, p=0.05). When comparing the work status of patients without social security, a significant increase was observed in the work status at baseline and after kidney transplantation (23.7% vs 45.8%, p=0.001).

Conclusions: Access to kidney transplantation in Mexico is uneven and this is due to the fragmented health system in Mexico. A national kidney transplant program without inequities is required where the entire population has access to health services and their post-transplant follow-up.
PO2151
Outcomes of Kidney Referrals from Donors with High Infection Risk in the Most Populous Donor-Specific Antibody
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University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Background: Overdose-death donors (ODD) increased from 1.1% of donors in 2000 to 13.4% in 2017. Kidneys from ODDs were discarded at a higher rate than trauma-death donors. US Public Health Service defines organs from individuals with opioid abuse as being at increased risk of infection with HIV, HepB and HepC. CAOP is the most populous DSA in the country and improving utilization of organs within the DSA is of great importance. We aimed to study the utilization of kidneys from High-Infectious Risk Donors in this DSA.

Methods: We obtained data from UNOS and the Organ Procurement Organization (OPO), One Legacy between January 2015 and September 2020. We calculated the organ decline rate, organ refusal rate and rate of organs refused under the UNOS organ refusal code Donor age/quality and Donor Social History. We also compare these results to the trauma-death donors.

Results: Out of 2686 kidneys that were considered for recovery, 382 kidneys were from ODDs between 2015 and September 2020. 109 ODD kidneys (22.6%) were shared and successfully transplanted. 51 ODD kidneys were discarded locally in the DSA (22.2%). 47.5% were refused by centers due to “Donor Age, Quality and Social History” before being either transplanted or being discarded. 103 kidneys of the ODDS were not recovered or offered for transplant. 82 kidneys were recovered from Hepatitis C positive donors, out of which 52 (66.7%) were shared and transplanted outside the DSA and 15 were discarded locally.

Conclusions: Higher infectious risk increased risk donors were being shared and discarded at a high rate. Given we have more evidence that these higher infectious risk kidneys are transplantable efforts to improve their utilization are needed.

Funding: Private Foundation Support

PO2152
Lack of Insurance Predicts with Follow-up Deficiencies After Living Kidney Donation
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Background: Follow-up after living kidney donation in the United States has improved with recent policy mandates. We hypothesized that lack of insurance at donation may be a barrier to postdonation follow-up.

Methods: We examined Scientific Registry of Transplant Recipients (SRTR) data for 90,460 living kidney donors (LKD) in 2004-2018 to examine associations (adjusted odds ratio, aOR) of insurance status and other baseline factors with clinical and laboratory follow-up after donation.

Results: Follow-up increased over time, and was especially high in older LKD. Follow-up was lower in uninsured compared to insured LKD over time, including in the era of the Affordable Care Act (Fig A). In 2018, for uninsured vs insured LKD, respectively, clinical follow-up was 87.5% vs 90.4% at 6-months, and 76% vs 86.7% at 12-months, while 12-month lab follow-up was 55.4% vs 68.4%. In multivariate regression including adjustment for donation year and other baseline factors, uninsured status was associated with 7% lower odds of 6-month clinical follow-up (aOR, 0.93) and 14% lower odds of lab follow-up (aOR, 0.86). Follow-up was also significantly (P=0.05) lower for LKD who were African American (aOR 0.85) or Hispanic (aOR 0.91), unrelated to their recipient (aOR 0.85), not working (aOR 0.81) and with less than college education (Fig B).

Conclusions: While follow-up after living kidney donation is improving, uninsured LKD and those who are non-white, unemployed, and with lower education are less likely to receive follow-up. Novel initiatives are needed to provide access to follow-up care for at-risk LKD, including the uninsured and under-insured, to minimize the risk of socioeconomic disparities in long-term postdonation outcomes.

Funding: Other U.S. Government Support

PO2153
Visualizing Waitlist Outcomes for Kidney Transplant Candidates Whose Centers Have Declined Deceased Donor Offers
Cory Schaffhausen,1,3 Jon Miller,2 Arthur J. Matas,4 Ajay K. Israni,2,5 Andrew Wey,2 Allyson Hart,2 2Henepin Healthcare Research Institute, Minneapolis, MN; 3Scientific Registry of Transplant Recipients, Minneapolis, MN; 4Chronic Disease Research Group, Minneapolis, MN; 5University of Minnesota Department of Surgery, Minneapolis, MN.

Background: While transplant centers closely monitor posttransplant outcomes for each transplant recipient, centers currently lack data to monitor waitlist outcomes of individual candidates. Waiting candidates may receive multiple deceased donor organ offers. Centers may decline offers on behalf of the candidate in order to wait for a better offer. These decisions may impact waitlist outcomes because a better offer may not arrive, and dialysis-related morbidity may worsen. We sought to develop waitlist outcome reports to facilitate monitoring of candidates receiving donor offers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: A report mockup used patient-level data from the Scientific Registry of Transplant Recipients (SRTR). Data included a deidentified random sample of 200 kidney waitlist candidates from across the United States who had received at least one offer between May 7, 2019 and May 6, 2020. For each candidate, offers were identified from match runs from January 1, 2014 to May 6, 2020. Match run data included any offer that was ultimately accepted somewhere and resulted in a transplant. Offers in the match run after the last accepted offer and multi-listed candidates were excluded.

Results: The report visually identifies several outcomes: candidates who died after receiving offers, additional time on dialysis, and changes to quality and frequency of donor offers over time. Figure 1A depicts multi-listed patients on a waitlist. Each horizontal row represents one candidate, and each colored cell represents the highest-quality donor offer for each month, indicated by Kidney Donor Profile Index (KDPI). Additional research is warranted to evaluate additional relevant candidate and donor data for reports (eg, offer number) and understand the utility of visual representations of the impact of offer decisions made on behalf of waitlist candidates.

Conclusions: The waitlist reports are a potential method for centers to self-monitor candidates and may supplement posttransplant outcome monitoring and existing decision support tools such as statistical outcomes calculators. The reports illustrate how offer frequency and KDPI change while candidates wait, as well as candidates’ disburden. Acceptance criteria at most transplant centers for waitlisting include BMI. The best approach to weight loss to facilitate active listing is unknown. A conservative weight loss approach was ineffective in most kidney transplant candidates with diabetes treated conservatively for obesity for 1-year post weight loss consultations, where the surgical and non-surgical weight loss options were discussed. A comparator group (n= 15) included patients with the mean BMI of 43.1 (4.4) who had bariatric surgery by 1 year post consultation. Options were discussed. A comparator group (n= 15) included patients with the mean BMI of 43.0 (4.8), and total body weight loss was 4.4 (8.2) kg (3.6% (6.5). BMI has not improved at 2 years (p=0.8; Figure 2A). Eighteen patients (64%) remained ineligible for a transplant due to excess weight and/or comorbidities over a mean follow-up of 4.2 (9.9 years). Most patients (75%) did not achieve an acceptable BMI for transplant. In contrast, total body weight decreased by 22.18 (10.1) kg (19% (7%)) at 6 months post-bariatric surgery with the BMI of 34.2 (4) and 32.5 (3.7) at 6 and 12 months, respectively (Figure 2B). Bariatric surgery was associated with subsequent kidney transplantation (HR = 5.75; CI [1.49, 22.14], p < 0.01).

Conclusions: A conservative weight loss approach was ineffective in most kidney transplant candidates with diabetes to access into transplantation. These data suggest the need for larger controlled trials.

Baseline characteristics

Data presented as Mean (SD), or % (n). BMI=body mass index.

PO2154
Guiding Kidney Transplant Candidates for Effective Weight Loss

PO2155
Risk Factors and Outcomes of Post-Transplant Erythrocytosis Among Adult Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

PO2156
Efficacy of Sodium Zirconium Cyclosilicate for Treatment of Acute Hyperkalemia in Solid Organ Transplant Recipients

Forest plots of the included studies assessing the association between PTE in KT patients and outcomes of (A) Overall mortality, (B) DCGF, (C) Thromboembolism

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2157
Clinical Characteristics and Outcomes of FSGS in Kidney Transplant Recipients: A Single-Center Experience
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Background: Focal segmental glomerular sclerosis (FSGS) is a common etiology of chronic kidney disease in adults. Many progress to end stage renal disease requiring dialysis initiation and/or renal transplantation. It is also known to recur in transplantation, however there is limited literature addressing treatment options and outcomes in these patients. The purpose of this study is to evaluate clinical characteristics and post-transplant outcomes in kidney transplant recipients (KTRs) with primary and secondary FSGS.

Methods: This is a single-center retrospective study where data was collected from November of 2014 to December of 2020 on all KTRs with the diagnosis of FSGS within the Henry Ford Health System in Detroit, MI.

Results: A total of 39 KTRs were studied. 28% had primary FSGS and 71% had secondary. Baseline characteristics of KTRs can be found in table 1. In this single center study, these findings are important in understanding the utility of ZS-9 broadly in SOT recipients.

Funding: Other NIH Support - REDCap use funded by UL1 TR000445 from NCATS/NIH

Table 1

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>11 (62.5)</td>
<td>28 (71.75)</td>
</tr>
<tr>
<td>Rejection at PT</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Age at time of diagnosis (y)</td>
<td>35 (23-52)</td>
<td>34 (19-72)</td>
</tr>
<tr>
<td>Age at time of remission (y)</td>
<td>35 (23-45)</td>
<td>35 (28-77)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (63.6)</td>
<td>23 (75.8)</td>
</tr>
<tr>
<td>BMI</td>
<td>30 (28-31)</td>
<td>30 (20-42)</td>
</tr>
<tr>
<td>African American</td>
<td>11 (100%)</td>
<td>8 (28.6%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4.09 (2.95-5.3)</td>
<td>1.36 (0.69-2.48)</td>
</tr>
<tr>
<td>Time of diagnosis to ESRD (mo)</td>
<td>45 (0.14)</td>
<td>45 (0.22)</td>
</tr>
</tbody>
</table>

Unless noted, table entries are frequency (%) or mean +/- SD.

Conclusions: ZS-9 for treatment of acute hyperkalemia in hospitalized SOT recipients was efficacious and safe in this single center study. These findings are important in understanding the utility of ZS-9 broadly in SOT recipients.
PO2159
Outcomes of Renal Transplantation in Patients with AL Amyloidosis: An International Collaboration Through the International Kidney and Monoclonal Gammapathy (IKMG) Research Group
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Background: New systemic therapies that successfully suppress toxic light chain production have led to an increase in the number of patients with AL amyloidosis who survive longer albeit with end stage renal disease. There is a critical need to identify patients in this specific population who can have good outcomes with renal transplantation.

Methods: We pooled data from 237 patients from 5 countries with AL amyloidosis who underwent renal transplantation between 1987 and 2020. Cox regression analysis and Kaplan–Meier method were used.

Results: The majority of the patients (62%) underwent high dose melphalan and autologous stem cell transplantation (HDMAST) prior to renal transplantation. Overall survival from the time of transplantation was 8.6 years with a median follow-up of 8.5 years. One-, three- and five-year OS from renal transplantation was 95%, 83% and 73%, respectively. The median time of graft survival was 7.8 years. Death censored graft survival at one-, three- and five-year was 79%, 69% and 69%, respectively. Survival outcomes were analyzed based on degree of hematologic response to therapy at the time of renal transplantation. Overall and graft survival were better in patients with complete hematologic response and very good partial response (CR+VGPR) compared to partial response, no response or treatment naïve patients (P<0.01). Graft survival in CR+VGPR group (median time not achieved vs 10 years, p=0.001) and the time to amloidic recurrence was significantly longer in the CR+VGPR group (median time not achieved vs 10 years, p<0.001). Comparing CR vs VGPR there was no difference in OS and graft survival. A total of 69 patients (29%) experienced hematologic relapse requiring treatment post renal transplantation. Graft survival for those who had a hematologic relapse was not statistically different from that of patients without relapse. Successful hematologic treatment prevented graft loss in 87% of patients who had amloidic recurrence in the graft.

Conclusions: Our results show that selected patients with AL amyloidosis undergoing kidney transplantation have good outcomes.

PO2160 Primary Hyperoxaluria Type 2: Is Combined Liver Kidney Transplant the Answer?
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Introduction: Primary Hyperoxaluria (PH) is a group of rare inborn errors of glyoxylate metabolism characterized by overproduction of oxalate. Oxalate is rarely soluble and is deposited as calcium oxalate in various organs, with the kidneys being the prime target leading to ESRD.

Case Description: 60-year-old female with a history of diabetes, hypertension and osteoporosis is being evaluated for end stage renal disease. Patient has undergone 4 renal biopsies over the last 3 years and has developed interstitial calcifications. Genetic testing for PH type-2 was positive and patient was started on allopurinol and a calcium reducing diet.

Discussion: PH type-2 is thought to have a more favorable prognosis than PH type-1.10,11 However, patients are at risk for developing recurrent oxalate deposition and may require additional therapy. Currently, there is no definitive standard of care for PH type-2, but a combination of medical and surgical management is often utilized. In this patient, a combination of a calcium reducing diet and allopurinol were able to achieve an oxalate level of 15. Patient finally recovered her kidney function almost 4 months later with clearance of oxalate crystals. Patient is currently off dialysis and taking daily oxalate binders.

Conclusions: PH type-2 has led to early post-transplant renal function loss. Dhondap and Del Bello each reported a case of successful treatment of PH type-2 with simultaneous liver-kidney transplantation. Similarly, while our patient remained dialysis dependent for almost 4 months post combined liver-kidney transplant, she is now successfully off dialysis. These 3 cases support the idea of a combined liver-kidney transplant as a better option for PH type-2.

PO2161 Early Post Renal Transplant Hypertension: Incidence of Masked Hypertension and Hemodynamic Correlates
Viavakumar Paramasivam, Barbara A. Greco, Spencer Hodgins. Baystate Medical Center, Springfield, MA.

Background: Hypertension following renal transplantation is prevalent and impacts long term graft survival. Masked and white coat hypertension have been reported in patients with renal allografts. The onset and mechanism of masked hypertension in these patients is poorly understood. We report preliminary data from an ongoing prospective observational study of HTN in the early post-transplant period.

Methods: A total of 40 patients post-renal transplant were evaluated for 1, 3, and 5 months post-transplant. At the same time periods, blood pressure measurements including standing and sitting blood pressure, and a 24-hour ambulatory blood pressure monitoring were performed. Systolic and diastolic blood pressures were measured on tablet devices at 15 minute intervals for 24 hours.

Results: Of the 40 patients analyzed, 33 of 40 patients completed ABPM at 1 month and 16 completed the 3-4 months post-transplant. Mean office BP at visit 1 and 2 were 133/79 and 132/78, respectively. At the same time periods, bioimpedance measures including cardiac index (CI), total peripheral resistance (TPR) and total body water (TBW), were obtained using a whole body bioimpedance technology (NiCAStm). Patient demographics, office blood pressures (BP), ABPM and bioimpedance data were analyzed to determine factors that contribute to masked and white coat hypertension.

Conclusions: In this preliminary analysis of a prospective observational study, we observed an increase in the rate of masked hypertension as patients get beyond 3 months post transplant. A significant percentage of these post transplant patients have non-dipping hypertension. Using whole body bioimpedance technology, we did not identify differences in hemodynamic parameters between the 1 and 3 month time periods and between those with and without masked HTN.

PO2162 AKI Caused by Early Post-Kidney-Transplant Nephrocalcinosis Related to Severe Tertiary Hyperparathyroidism
Nicole Nguyen,1,2 Daniel E. Neri,3 Sergio A. Trevino Manilo,1,2 Mourad Aliabbagh,1,2 1The University of Texas Rio Grande Valley, Edinburg, TX; 2DHR Health, Edinburg, TX.

Introduction: Persistent hyperparathyroidism is a common condition in post-kidney transplantation. We present a case of acute kidney injury (AKI) caused by nephrocalcinosis due to tertiary hyperparathyroidism in an early post-transplant patient, which was managed and improved with parathyroidectomy.

Case Description: A 42-year-old male with a history of diabetes mellitus, hypertension and a deceased donor kidney transplant 3 months prior was evaluated for hypercalcemia. Medications included nifedipine, insulin, misoprostol and prednisone. Cincaceltat was started but calcium (Ca) level continued to rise. He was later hospitalized for AKI, cinacalcet was discontinued. Blood work showed creatinine (Cr) 2.6 mg/dl, baseline Cr 1.29 mg/dl, corrected Ca 9.9 mg/dl, and tacrolimus 6.2 mg/L. Images of the kidney graft were negative for obstruction. Kidney biopsy revealed no acute rejection or BK infection. However, there were findings of acute tubular injury with frequent calcific intratubular casts and interstitial fibrosis, tubular atrophy involving 30-40% cortical surface. Interestingly, kidney biopsy obtained 2 months prior was unremarkable. Further workup showed parathyroid hormone 1220 pg/mL, 1,25 di-OH vitamin D 20.1 pg/mL. Given the rapid decline in kidney function and biopsy changes, subtotal parathyroidectomy was performed during the same admission. At 2-week follow-up visit, Cr improved to 1.5 mg/dl.

Discussion: Persistent hyperparathyroidism in post-kidney transplantation can lead to hypercalcemia with nephrocalcinosis, increased mortality and graft loss. These patients usually failed medical therapies. Our case demonstrates that early parathyroidectomy is the treatment of choice for patients with severe hyperparathyroidism and symptomatic hypercalcemia.
Kidney biopsy in Nephrocalcinosis - Acute tubular injury with calcium phosphate deposits, interstitial fibrosis and tubular atrophy

PO2163
A Rare Case of Liver Failure in a Kidney Transplant Recipient with Polycystic Kidney Disease
Laila S. Lakhani, Payaswini Vasanth. Emory University School of Medicine, Atlanta, GA.

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) patients usually have great outcomes post kidney transplant. We describe a rare case (none reported in literature), where kidney transplantation led to progressive enlargement of liver cysts and liver failure physiology.

Case Description: A 51 year old female with end-stage kidney disease from ADPKD, underwent a deceased donor kidney transplant in July 2020. She was induced with basiliximab and maintained on Belatacept, Tacrolimus, mycophenolate and prednisone, asanth. This complex hospitalization culminated into her demise secondary to cardiac arrest.

Discussion: This is a very challenging yet fascinating case that highlights progressive liver failure from rapidly enlarging liver cysts within 3 months of kidney transplantation. Did immunosuppression contribute to accelerating the growth of liver cysts? Should a select group of patients with ADPKD be evaluated for combined liver and kidney transplantation? Multi-disciplinary discussions between transplant nephrologists, hepatologists, and surgeons can guide decision making in these complex patients.

PO2164
Association Between Recipient-Donor HLA Genotypes and Recurrent Membranous Nephropathy After Kidney Transplantation
Edmund Y. Chung,1 Katrina Blazek,2 Ankit Sharma,3 Siah Kim,4 Armando Texeira-Pinto,2 Germaine Wong,5,6 Stephen I. Alexander.1 1Children’s Hospital at Westmead Centre for Kidney Research, Westmead, NSW, Australia; 2The University of Sydney, Sydney, NSW, Australia; 3Westmead Hospital, Westmead, NSW, Australia.

Background: Recurrent membranous nephropathy (MN) occurs in up to 40% of kidney transplant recipients (KTRs) and is a major cause of graft loss. Recipient alleles at the HLA-D loci were found to have an increased risk of disease recurrence in KTRs with primary MN. However, the association between recipient-donor HLA characteristics and disease recurrence has not been explored.

Methods: We integrated data from two registries: United Network for Organ Sharing, and Australian and New Zealand Dialysis and Transplant registries between 1963 and 2020. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for variable selection. The penalization parameter was chosen by cross-validation and the covariates with non-zero coefficients were included in a logistic regression, together with class, and fitted using maximum likelihood. The model performance was evaluated using C-statistics.

Results: 8058 KTRs with primary MN were included and 232 had recurrent MN. Of the 266 variables, group LASSO selected 59 variables considered as variables of importance and were included in the adjusted logistic regression model. Recipient HLA genotype at DR11 (odds ratio, 95% confidence interval) (1.81, 1.30-2.51, p<0.001), B38 (1.93, 1.00-3.45, p=0.04), and B46 (6.75, 1.55-26.30, p=0.007) and donor-recipient HLA-B65 match (3.38, 1.07-8.85, p=0.02) were associated with an increased risk of recurrent MN, adjusted for recipient sex, ethnicity, comorbidities (diabetes, hepatitis C and cancer), immunosuppression regime (T cell depletion induction therapy, B cell depletion induction therapy, tacrolimus, corticosteroid, or other maintenance therapy).

Conclusions: Recipient HLA-DR11, B38, B46 and donor-recipient HLA-B65 match were associated with an increased risk of recurrent MN in KTRs.
Successful En Bloc Liver Kidney Transplant in a Morbidly Obese Patient
Paola Varas, Joseph T. Leuds, Shawn Pelletier, Nicolas Goldaracena, Angie G. Nishio Luca. University of Virginia, Charlottesville, VA.

Introduction: En bloc liver and kidney transplant is a variant for the traditional simultaneous liver kidney transplant (SLKT) technique that, with simultaneous reperfusion of both grafts through a common vascular anastomosis, can decrease operative time, cold ischemia time and risk of surgical site infections.

Case Description: A 50-year-old morbidly obese (BMI >50) male with history of ESRD due to hypertension, on hemodialysis for 4 years, decompensated NASH cirrhosis, Factor V Leiden, previous episodes of venous thromboembolism and obstructive sleep apnea presented for SLKT. The donor was brain dead with a KDPI 22%, anatomy was normal. On backtable, the donor right renal artery and splenic artery were anastomosed end-to-end to leave these arterial systems in continuity and perfused from the celiac trunk. The infrarenal IVC cuff was sutured using an endovascular stapler to close the left renal venous return. Direct technique with a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both allografts from the arterial inflow followed by the venous inflow (Fig. 1B). Direct flow assessments by doppler was excellent. The ureter was anastomosed to the recipient’s right native ureter in an end-to-side fashion followed by a double J ureteral stent. Total operative time was 7 hrs, 10 min, CIT 7 hrs and WIT 46 min. The postoperative course complicated by DGI for 3 weeks. He was discharged home on POD 6 and the ureteral stent was removed on POD 48. At 3 months follow-up, the portal vein and renal artery remain patent and both allografts have excellent functioning without evidence of complications.

Discussion: This case illustrates that en block liver kidney is a feasible and effective option for well-selected patients. This technique should be considered in obese patients or those with extensive iliac arteries atherothrombosis who have increase morbidity with transplant and could benefit from single surgical incision. Close post transplant monitoring is key to surveil for potential complications.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

P2O2167
Little Goes a Long Way: Is Kidney Donor Profile Index (KDPI) a Good Predictor for Pediatric Kidney Donors Less Than 10 kg? Lilia Harris, Uma Mahesh R. Avula, Bushra Syed, Pradeep Vaitha, Franco H. Cabeza Rivera. The University of Mississippi Medical Center, Jackson, MS.

Introduction: Pediatric deceased donor kidneys (DDK) constitute 10-12% of the DDK supply and are allocated using the same criteria as adult kidneys. Kidney Donor Profile Index (KDPI) is designed to predict kidney graft performance in adult recipients based on 10 donor characteristics. A KDPI scale goes from 1 (best) to 100 (worst). Most child donor kidneys classified as KDPI-D (<5%) and KDPI-C (<5%) which makes them less desirable. In addition, few programs use kidneys from donors less than 1 year.

Case Description: We report a case of pediatric en bloc kidney (EBK) transplantation procured from a 7-month-old female donor, with a bodyweight of 7.7 kg. KDPI is 87%. The recipient is a 59-year-old female with a bodyweight of 54 kg and a diagnosis of ESKD secondary to biopsy-proven FSGS. The recipient had been on PD for 37 months, baseline sCr of 12-15 mg/dL and was oliguric. Cold ischemic time of the kidneys was 8 h 33 mins, warm ischemic time - 24 mins, estimated blood loss - 200 mL. Intraoperative challenges included tedious organ preparation and extremely small vessels requiring complex reconstruction along with the creation of 2 ureteral anastomoses. A postoperative complication included delayed graft function required 2 hemodialysis sessions. Thereafter graft function improved and sCr trended from 15.48 mg/dL to 1.46 mg/dL at 4 weeks follow-up.

Discussion: KDPI is a valuable tool for adult donors but takes an oversimplified approach to the pediatric donor population. KDPI calculation includes donor age, weight, and height does not lead to a proportional scaling of the hazard in pediatric donors. It leads to misclassification and underestimation of a sizable number of kidneys from small pediatric donors. In addition, although it was found en bloc to be a significant factor and shown EBK versus SKT as an important predictor for graft performance, it was decided not to include this criterion in KDPI. Pediatric EBKs had the lowest acute rejection and delayed graft function rates in comparison with SKT. Furthermore, the cGFR for pediatric EBKs improves due to the continuous growth of pediatric kidney allografts. In summary, modified KDPI tailored to the pediatric donors is warranted to accurately represent pediatric donor kidney survival, attract recipients and surgeons to address the problem of organ shortage.

PO2168
Pickering Syndrome in a Kidney Transplant Recipient Jad Tabbara, Mohamed Hassanein, Omar A. Aleter, Joshua J. Augustine. Cleveland Clinic, Cleveland, OH.

Introduction: Pickering syndrome (PS) refers to hypertensive urgency with recurrent flash pulmonary edema (FPE) due to bilateral renal artery stenosis (RAS) or unilateral RAS in patients with a solitary kidney or kidney allograft. We report a case of PS in a kidney transplant recipient.

Case Description: A 68-year-old gentleman with a history of end-stage kidney disease secondary to diabetic nephropathy treated with deceased donor kidney transplantation (on Belatacept, Mycophenolate Mofetil, and Prednisone) and a history of chronic heart failure with reduced ejection fraction for FPE presented 3-months post kidney transplantation with hypertensive urgency, acute kidney injury (AKI) and FPE. Blood pressure was 170/85 mmHg and serum creatinine was 2.5 mg/dL (baseline 1.8 mg/dL). Echocardiogram showed preserved left ventricular function. Kidney transplant ultrasonography (US) showed a dense vasculature with no hydronephrosis. Kidney biopsy showed no evidence of acute rejection. Duplex ultrasound showed a high proximal peak systolic velocity (PSV) 622 cm/sec and a low renal arterial resistive index (RI = 0.55) with severe (60-99%) stenosis. An intravascular-ultrasound (IVUS) guided stent placement facilitated safe renal artery revascularization using only 2 mL of contrast agent subsequently leading to a complete resolution of AKI and no further episodes of FPE.

Discussion: Transplant RAS causes 1-5% of post-transplant hypertension, and usually occurs within the first 6 months post-transplantation. Activation of the renin-angiotensin-aldosterone system leads to worsening hypertension, allograft dysfunction and fluid retention with FPE. Although duplex US is used for screening, angiography with simultaneous percutaneous angioplasty is often needed for definitive diagnosis and treatment. IVUS guided stenting is beneficial in patients with AKI to minimize contrast exposure and further worsening of graft function. Early diagnosis and prompt treatment of PS are the key to minimize morbidity and mortality in these patients.

PO2169
Treatment of Transplant Renal Vein Thrombosis in a Pediatric Patient Using an EkoSonic Endovascular System (EKOS) Catheter Siddharth A. Shah, Malavika Prasad. Pediatric Nephrology team University of Louisville, Louisville, KY.

Introduction: Transplant renal vein thrombosis (oRVT) is a critical complication after renal transplant with reported prevalence of 0.1% to 4.2% leading mostly to graft loss. Thrombolytic therapy and surgical thrombectomy has been described previously to treat iRVT. EKOS is a modern and innovative ultrasound-facilitated catheter directed thrombolytic technique that is approved primarily for treatment of pulmonary thrombosis, deep vein thrombosis and arterial occlusion. It requires ultrasound core wire and infusion catheter for delivery of fibrinolytic agent such as Tissue plasminogen activator (tPA).

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The ultrasound core wire or transducer generates ultrasound waves that help accelerate fibrinolysis, decrease the treatment time, and decrease the risk of bleeding. The use of EKOS for IRVT has not been reported in pediatric literature and we describe one such case.

Case Description: We describe a 17-year-old boy with history of congenital nephrotic syndrome and donor renal transplantation in 2005. His post-transplant course was complicated by multiple episodes of deep venous thrombosis in right lower extremity, chronic right inguinal venous thrombosis with collaterals in lower extremities, maintained on anticoagulant therapy. He presented with serum creatinine elevation of 3.7 mg/dL (baseline of 1.4 mg/dL) and anuria. On renal US Doppler, the transplant venous system was not seen and there was concern of lack of flow/RTV. CT venogram performed showed acute renal occluding thrombus in left lower extremity venous system extending from left popliteal and femoral vein all the way to the left transplant renal vein in the left iliac fossa with no evidence of ICA as per hematology without any improvement. Active discussions between hematology, nephrology, and vascular surgery led to a trial of EKOS device to salvage the allograft. The patient then underwent thrombolysis using EKOS catheter with peripheral access to the left transplant renal vein, without any complications. The repeat renal US Doppler showed patent left renal transplant vein, with continued occlusion in the left external iliac vein. The serum creatinine returned to baseline 1.4-1.5 mg/dL one week after procedure.

Discussion: We describe a novel report of successful treatment of transplant renal vein thrombosis using EKOS catheter. Further studies are needed to provide more insight in this therapy.

PO2170
Reversal of Prolonged Delayed Graft Function Following Kidney Transplantation with a Belatacept-Based Regimen
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Introduction: Delayed graft function (DGF) following kidney transplantation is associated with adverse graft and patient outcomes. Many factors contribute to the development of DGF including ischemia-reperfusion injury. There is concern that calcineurin inhibitors such as tacrolimus can perpetuate DGF through tubular injury and vasoconstriction. The non-nephrotoxic co-stimulation blocker belatacept could potentially be beneficial in improving allograft function in such scenario. We present a patient who experienced prolonged DGF following kidney transplantation that reversed following switching immunosuppression from a tacrolimus-based to belatacept-based regimen.

Case Description: A 73-year old non-sensitized female with a history of coronary artery disease, hypertension, and type 2 diabetes mellitus on maintenance hemodialysis underwent kidney transplantation from a 63-year old brain-dead donor with acceptable procurement kidney biopsy and kidney donor profile index (KDPI) of 88%. Cold ischemia time was 27.5 hours. She received induction with Thymoglobulin followed by tacrolimus/mycophenolic acid maintenance with early steroid withdrawal. In the perioperative period, she experienced hemodynamic instability from cardiacogenic shock requiring prolonged ICU stay. She developed DGF requiring dialysis support. Despite clinical improvement, she remained dialysis-dependent. Allograft biopsies at 2 weeks and 2.5 months post-transplant showed acute tubular injury and no rejection. Four months from transplant, immunosuppression was changed from tacrolimus-based to belatacept-based regimen. One week after this change, the urine output started improving and 10 days later the patient came off dialysis. Her serum creatinine continued to improve with a measured value of 2.4 mg/dL and excellent urine output 3 weeks since stopping dialysis.

Discussion: The patient experienced very prolonged DGF after receiving a high KDPI kidney. We believe that replacing tacrolimus with belatacept facilitated the reversal of prolonged DGF and freedom from dialysis in this patient. Conversion of tacrolimus to belatacept in kidney transplant recipients experiencing prolonged DGF and utilization of de novo belatacept-based maintenance regimens in patients at high risk for developing DGF should be considered in order to improve graft and possibly patient outcomes.

PO2171
Disease-Specific Tissue RNAs as Diagnostic Tool for Kidney Transplant Pathology
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Background: MicroRNAs (miRNAs) play an important role in the development of renal diseases as epigenetic regulators of gene expression. However, there are limited data on tissue miRNA expression in transplantation-related kidney disease.

Methods: Study enrolled fifty-six transplant kidney patients with surveillance indication kidney transplant biopsy including pretransplantation biopsies, which were divided into four (four + control) groups. The control group (CG, n = 12) consisted of patients without pathohistological changes on surveillance biopsy. Patients with indication biopsy due to an increase in serum creatinine and nonspecific chronic changes in pathological analysis were in the nonspecific group (NS, n = 6). The other three groups consisted of histologically proven antibody-mediated rejection (ABMR, n = 13), recurrent glomerulonephritis (rGN, n = 15), and acute tubular injury/necrosis (ATN, n = 10). We analyzed the expression of 6 selected miRNAs (miR-29c, miR-126, miR-146a, miR-150, miR-155, miR-223) and compared them with the respective disease process.

Results: When comparing mRNA expression before and after transplantation, there was no statistically significant difference in the expression of the analyzed miRNAs in CG, NS and rGN, but we observed a statistically significant change in the expression profile of miR-146a and miR-155 after transplantation in patients with ATN and ABMR. Post-transplant biopsies showed differential expression of miR-146a and miR-155 in ABMR and NS compared to CG, miR-146a in ATN compared to CG and miR-223 in NS compared to CG. All but miR-146a showed differential expression in pretransplantation biopsies before transplantation of either NS, rGN, ABMR or ATN compared to CG, but the difference in expression after transplantation was more pronounced.

Conclusions: Our results suggest that miR-146a and miR-155 play an important role in pathological processes after kidney transplantation and also support the hypothesis that there are differences at the molecular level of the donor kidney that may predispose the kidney to certain types of pathohistological damage.

PO2172
Trajectory of Gene Expression Profile and Donor-Derived Cell-Free DNA Before and After Subclinical Acute Rejection
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Background: Subclinical acute rejection (subAR) is associated with poor kidney allograft outcomes. Blood gene expression profile (GEP) and donor-derived cell-free DNA (dd-cfDNA) have been used to exclude or diagnose kidney allograft rejection non-invasively. However, the trajectory of GEP and dd-cfDNA are unknown after subAR. We investigated the changes in GEP and dd-cfDNA after subAR.

Methods: We analyzed 100 subjects with GEP and 87 with dd-cfDNA, with some subjects in both groups. GEP and dd-cfDNA were performed before, at, and after the time of subAR. The cohort was extracted from a previously reported prospective, multicenter observational study. GEP was performed using a microarray-based 120 gene expression profile. The study reported dd-cfDNA as a percentage of donor cell-free DNA over total cell-free DNA. Locally estimated scatterplot smoothing (LOESS) and linear mixed effect models were used to analyze longitudinal changes of GEP and dd-cfDNA scores.

Results: A total of 1,314 blood samples were assessed. The longitudinal changes of GEP scores at a sample level are shown in Figure 1. GEP scores peaked at the time of subAR and decreased after. The slope of GEP scores was significantly different after subAR (slope difference = -0.201 p-value <0.001) (Figure 2). On the other hand, dd-cfDNA continued to rise even after subAR (Figure 1). There were no significant changes to the slope of dd-cfDNA between pre-subAR and post subAR (p-value = 0.98) (Figure 2).

Conclusions: GEP scores significantly dropped, while dd-cfDNA persistedly increased after subAR. How this may inform the biology of gene expression vs. dd-cfDNA after treatment of rejection requires additional study.

Funding: Commercial Support - Viracor-Eurofins
Methods: In this small, retrospective cohort study, we examined the results of TruGraf in 48 kidney transplant recipients with stable graft function (median 12.9 mo posttransplant, IQR 5.9-19.8). Patients were maintained on TAC/MMF +/- prednisone. We collected data on 11 biopsies, 17 dd-cfDNA, and 16 DSA assays performed within 1 mo of TruGraf.

Results: There were 34 ‘TX’ and 14 ‘Not-TX’ results. 3 pts in former (1 with TCMR) and 8 in latter group (1 TCMR, 3 ABMR) had biopsies. Among those with DSA testing, out of 7 ‘Not-TX’ cases 2 had DSA, compared with 4 out of 9 with ‘TX’ (p=0.45). Combining biopsy results with DSA, ‘rejection or DSA’ was present in 5/8 of ‘Not-TX’ and 4/9 of ‘TX’ groups (p=0.4). dd-cfDNA >1% was seen in 1/6 of ‘Not-TX’ and 2/17 of ‘TX’ cases, and 2/6 and 8/17, respectively, had values >0.5% (p=0.46). Comparing dd-cfDNA >0.5% and TruGraf, the former had 3/6 vs 4/6 negative results in absence of ‘rejection or DSA’; while positive results in presence of ‘rejection or DSA’ was seen in 4/6 vs 2/6, respectively.

Conclusions: These preliminary observations in our cohort suggest that TruGraf could be a useful non-invasive tool for monitoring of allograft status in kidney transplant recipients. With implementing protocolized use of this test in our center along with dd-cfDNA and DSA screening at various time points, we will continue to prospectively collect data, and will be able to better define its utility in our center toolbox.

Funding: Clinical Revenue Support

PO2174

Sparse Intragraft Molecular Classifiers for Antibody-Mediated and T Cell-Mediated Kidney Transplant Rejection: Development, Validation and Clinical Value

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Background: Although the transcriptional landscapes of antibody-mediated rejection (ABMR) and T-cell mediated rejection (TCMR) have been largely elucidated, applying these gene signatures in transplant clinics is hampered by the large number of features and difficult integration with histological findings. We aimed to develop and validate a sparse molecular classifier for ABMR and TCMR.

Methods: In a discovery cohort of 224 kidney transplant biopsies, microarray gene expression was applied to build two separate prediction models for presence of ABMR or TCMR. Variable selection for logistic regression was performed by lasso regularization. The diagnostic accuracy and prognostic value of the obtained ABMR and TCMR classifiers were assessed in two external validation cohorts.

Results: From the discovery cohort, a 2-gene ABMR classifier (PLA1A, GNLY) and 2-gene TCMR classifier (IL12RB1, ABPC18) were derived. In the first validation cohort (N=403 biopsies), diagnostic accuracy was retained for both ABMR (ROC-AUC 0.80, 95% CI 0.75-0.85) and TCMR (ROC-AUC 0.83, 95% CI 0.77-0.89), also allowing discrimination between pure and mixed phenotypes. In the second validation cohort (N=282 biopsies), molecular ABMR and TCMR scores predicted graft failure (respective time-integrated AUC of 0.82 and 0.83) and identified kidneys at risk for graft failure which were not picked up by routine histology.

Conclusions: We identified and validated an intragraft 2-gene ABMR classifier and 2-gene TCMR classifier that can be used as diagnostic and prognostic tools. Robust variable selection models can yield parsimonious molecular classifiers for kidney transplant rejection, facilitating their interpretation and clinical implementation.

PO2175

Evolving Experience with TruGraf® Gene Expression Profile and TRAC™ Donor-Derived Cell-Free DNA Testing in Kidney Transplantation: First Year Post Transplant and Beyond

Vijayakumar Paramasivam, Barbara A. Greco, Michael J. Germain. Baystate Medical Center, Springfield, MA.

Background: Non-invasive validated rejection biomarkers are available to monitor kidney transplant recipients (KTR). Our program has replaced 3 and 12 month protocol biopsies (BX) with biomarker surveillance using TruGraf (TG) gene expression profile (GEP) validated to rule out subclinical acute rejection (subAR) and TRAC donor derived cell free DNA (dd-cfDNA) as a marker of allograft injury. This is the evolving single center experience of TruGraf-TRAC surveillance for KTR within the 1st year post-transplant (post-txp) and beyond.

Methods: Our immunosuppression (IS) protocol is alentuzumab with tacrolimus maintenance, mycophenolate mofetil added in high risk KTR. TR and TG were done at 3, 6 months post-txp and in all changes (n=3/TORI/tolmetin, IS decrease). Additionally, all KTR to be tested at least once to determine baseline status (immune quiescence). A positive (pos) TG, TR, or dynamic changes in post-op course prompts further evaluation and/or repeat TG/TRAC testing. BX were done in cases with equipos. Donor specific antibodies (DSA) tested in all patients.

Results: To date, 115 KTRs surveilled with TG and/or TRAC (149 TG and 90 TRAC tests). 30/41 KTR spared 3-month BX. Of 11 BX, 6 were for delayed/slow graft function (negative (neg) TG (Transplant eXcellence (TX)) and neg for acute rejection(DSA) and 5 were for pos TG (not-TX) with 3 neg for DSA/acute rejection. 12/16 KTRs avoided 1-year BX. 45 KTRs were > 1 year post-txp at testing (16 KTR > 10 years, 8 KTR >20 years). Table 1: TG/TRAC concordance (n=92). 45% concordant neg, confirming IS adequacy. 50% discordant (TG or TRAC pos) prompting eval and correlation with findings (DSA, proteinuria, renal failure). 5% concordant pos prompting BX, diagnosis, and/or subAR treatment.

Conclusions: Non-invasive TruGraf GEP with TRAC dd-cfDNA spares protocol BX in KTR at 3 and 12 months, while providing enhanced monitoring >1 year post-txp by ruling out subAR and assuring IS adequacy. Combined TruGraf and TRAC testing is promising, warranting larger studies for optimal synergy/frequency of serial testing, especially as subAR persists beyond the 1st year post-txp.

TruGraf/TRAC Concordance

PO2176

LIMS1 Risk Genotype and Clinicopathological Features of Kidney Transplant Recipients

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Background: LIM zinc Finger Domain Containing 1 (LIMS1) homozygous risk genotype (rs893403 GG) is associated with increased risk of T-cell mediated rejection (TCMR) after kidney transplantation (KTx). However, prior studies lack detailed histopathological data. We examined the association of LIMS1 genotype with histopathology of allograft rejection.

Methods: A total of 110 KTx recipients underwent allograft biopsy were genotyped for LIMS1 rs893403 variant by Sanger sequencing followed by PCR confirmation of the deletion. The 2013 Banff scores from allograft biopsies were compared between recipients homozygous for LIMS1 rs893403 genotype GG (n=24) versus AA/AG genotypes (n=86).

Results: There were no differences regarding demographic, clinical and laboratory features between the genotype groups (Table 1). Allograft biopsies were performed after a median 6.2 years after KTx. Serum creatinine, proteinuria and donor specific antibody levels at the time of biopsies were similar between groups. Banff median tubulitis score was significantly higher in GG group compared to AA/AG group (1.42±0.65 vs 1.12±0.66, p=0.03) (Figure 1). There were also no significant differences regarding histopathological diagnosis between the groups (Table 1).

Conclusions: Kidney transplant recipients with homozygous LIMS1 deletion had higher tubulitis scores. Our data supports the role of LIMS1 locus in the pathophysiology of allograft rejection and motivates ongoing work to elucidate mechanisms of association of LIMS1 risk genotype and allograft injury.
PO2177

Association of Vascular Endothelial Growth Factor Gene Polymorphism with Allograft Survival in Renal Transplant Recipients

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Background: Endothelial cell dysfunction is a primary cause for late allograft loss in renal transplantation recipients. Vascular Endothelial Growth Factor (VEGF) is a pro-angiogenic factor that has an important role in the development and maintenance of physiological function of endothelium cell thus may determines the allograft function.

Methods: We did genotyping of VEGF SNPs among 320 renal allograft recipients (non-rejecters (160) and rejecters (160)) by PCR- RFLP technique. Intragraft VEGF mRNA and protein expression were analyzed by RT-PCR and immunohistochemistry. Serum VEGF level were analyzed by ELISA.

Results: On comparison between donors and recipients genotypes of VEGF +936 C>T (CT (OR=7.16; 95% CI=4.33-11.84; P<0.00) and TT (OR=49.30; 95% CI=11.84-205.29; P<0.00)), -1190G>A [AG (OR=2.22; 95% CI=1.40-3.50; P=0.00), -1190G>A [GG (OR=2.34; 95% CI=1.34-4.10; P<0.00)], -2549 18bp Insertion/Deletion [ID (OR=2.35; 95% CI=1.38-3.99; P=0.002) and 18bp Deletion (OR=1.58; 95% CI=1.01-2.46; P=0.04)] were significantly associated with risk of rejection. On comparing mutant genotypes between non-rejecters and rejecters we found that genotypic frequencies of +936 C>T [TT (OR=2.43; 95% CI=1.33-4.44; P=0.004)], -1190G>A [GG (OR=1.94; 95% CI=1.03-3.67; P=0.04)], -2549 18bp Insertion/Deletion [ID (OR=1.58; 95% CI=1.01-2.46; P=0.04)] were significantly associated with risk of rejection. On comparing mutant genotypes between non-rejecters and rejecters we found that genotypic frequencies of +936 C>T [TT (OR=2.43; 95% CI=1.33-4.44; P=0.004)], -1190G>A [GG (OR=1.94; 95% CI=1.03-3.67; P=0.04)], -2549 18bp Insertion/Deletion [ID (OR=1.58; 95% CI=1.01-2.46; P=0.04)] were significantly associated with risk of rejection.

Conclusions: The present study signifies genetic associations of all the mutant genotypes of VEGF +936 C>T, -1190G>A, -2549 18bp Insertion/Deletion, and -1455T>C SNPs to be at increased risk for renal allograft rejection.

Funding: Government Support - Non-U.S.

PO2178

Machine Learning and Bioinformatics Approaches to Discover Urine Gene Expression Biomarkers for Kidney Transplant Rejection

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Background: While transplant biopsies are safe and accurate way for monitoring transplant progress, they are associated with defined risks and significant costs. Using the mRNA from urine, we proposed a non-invasive approach to diagnose acute rejection. The multi-step approach involved collection and mRNA analysis of urine samples, application of a machine learning algorithm to select an initial set of gene markers, adding known markers from prior work, and using the combined set for developing a final classifier. The classifier was developed on a training data consisting of 42 samples (17 rejection and 15 control) and a validation data set of 43 samples (13 rejection and 30 control).

Methods: RNA from urine samples was hybridized to customized NanoString panel, consisting of 796-gene Immune Profiling gene panel and 26 genes representing graft rejection or the development of fibrosis from published literature. The RNA samples were processed on the nCounter GEN2 using the high sensitivity protocol and high-resolution data capture. Raw data were imported into nSolver4.0 (NanoString) followed by log, gene counts and normalized data generation that was used in further analyses.

Results: Using Random Forest on NanoString data we first obtained a set of eight gene as our initial pool of markers. We combined them with the 20 gene markers from our previous work and developed a seventeen gene classifier (after removing duplicates and non-important genes). The combined signature of 17 genes had high AUC (0.875), accuracy (0.881), sensitivity (0.875), specificity (0.869), PPV (0.929) and NPV (0.857) on training data. Although the PPV dipped to 0.714 in the validation data, it still performed well resulting in high accuracy (0.84), sensitivity (0.77), specificity (0.87) and NPV (0.90).

Conclusions: This initial hybrid modeling approach has shown its significance and we plan to further strengthen its reliability and test robustness by incorporating more samples. The final classifier, a non-invasive approach to classify kidney graft health, could help improve serial monitoring of graft recipients while reducing the cost and safety risks associated with biopsies.

Funding: Other NIH Support - NIAID, Commercial Support - Eurofins-Viracor

PO2179

Discovery of Cellular and Genetic Signatures of Immune Tolerance in Kidney Transplant Recipients Through Single-Cell RNA Sequencing Analysis

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Background: Immune tolerance, defined by maintaining stable allograft function without immunosuppression after transplantation, is the ultimate goal of kidney transplant. Unlike bulk transcriptional analysis, single cell RNA sequencing (scRNA-seq) allows us to profile gene expression at the heterogeneous individual cell level. We aimed to investigate the difference of cellular and genetic signatures of immune tolerance in kidney transplant recipients (KTRs) through scRNA-seq analysis.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 13 KTRs with immune tolerance (Tol, n=5), biopsy-proven allograft rejection (Rej, n=4), and stable allograft function on maintenance immunosuppression (Stable, n=4) at a single transplantation centers. We used 20 cell surface marker antibody sequencing to cluster cell subsets, and 399 immune response panel to identify genetic expression difference at a single cell level. Single-cell distribution was visualized on UMAP plot.

Results: We generated 16,784, 10,180 and 7,280 single-cell transcriptomes of Tolerance, Rejection, and Stable groups, respectively. Tolerance cell clusters were identified using cell surface marker antibody. Heatmap hierarchical clustering showed distinct differential cell surface marker expression in Tolerance group in comparison with other groups. The fractions of B cells and regulatory T cells in peripheral blood were increased in Tolerance group, compared with other groups. The fractions of B cells and regulatory T cells in peripheral blood were increased in Tolerance group, compared with Rejection (fold change 0.12) and Stable group (fold change 0.30).

Conclusions: This is the first study to identify difference in cellular distribution and genetic expression of immune tolerance in KTRs at single-cell resolution so far. Taken together with further scRNA-seq analysis of immune tolerance, it would provide us a better understanding of biological pathways that develop immune monitoring strategy, and allow cessation of immunosuppression.

PO2180

Can a Combination of Blood Gene Expression and Donor-Derived Cell-Free DNA Improve Detection of Acute Rejection in Stable and Unstable Kidney Allograft Recipients?

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Background: Non-invasive biomarkers for the detection of acute clinical rejection or subclinical acute rejection (subAR) have shown modest diagnostic performance. Therefore, we hypothesized that a combination of gene expression profile (GEP) and donor-derived cell-free DNA (dd-cfDNA) would improve the diagnostic performance.

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666
PO2181

Lymphocyte Subpopulations in Clinical Practice After Kidney Transplantation: B Cell Levels Predict Renal Function at 1 Year
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Background: Lymphocytes subpopulations play a key role in the immune response after kidney transplantation. Many different T-lymphocyte have been studied for their suitability to monitor allograft rejection. B cells have been associated with acute and chronic antibody mediated rejection and with poor outcome after transplant but are associated with tolerant kidney transplant recipients.

Methods: We retrospectively analyze the lymphocyte subpopulation (total lymphocyte, CD3+, CD4+, CD8+, NK, CD20+) pre transplant, after 1 week, at discharge and after 2 months post transplant in a cohort of kidney transplant recipients and we evaluate the impact of this subsets on kidney outcome.

Results: 187 kidney transplant recipients were included in the study and a total of 748 samples were analyzed. We didn’t find any association between lymphocyte subsets and delayed graft function, primary non function and graft rejection. We found an association between low level of B lymphocyte at 2 months post transplant and 1-year GFR less than 45 ml/min (Table 1). The logistic regression combining these two assays achieved an AUROC of 0.80 significantly higher than 0.75 (GEP alone, p-value <0.001) and 0.72 (dd-cfDNA alone, p-value <0.01).

Conclusions: Combining the GEP and dd-cfDNA can improve the ability to distinguish acute rejection in both stable and unstable patients.

Funding: Commercial Support - Viraco-Eurofins

| Table 1: Diagnostic performance of GEP and dd-cfDNA for acute rejection including subAB |
|------------------|------------------|------------------|------------------|------------------|
| Sensitivity | Specificity | PPV | NPV | AUROC |
| GEP alone | dd-cfDNA alone | GEP alone | dd-cfDNA alone | GEP alone | dd-cfDNA alone | GEP alone | dd-cfDNA alone | GEP alone | dd-cfDNA alone |
| 0.74 (0.66-0.83) | 0.75 (0.68-0.81) | 0.74 (0.66-0.83) | 0.75 (0.68-0.81) | 0.74 (0.66-0.83) | 0.75 (0.68-0.81) | 0.74 (0.66-0.83) | 0.75 (0.68-0.81) |

PO2182

Inflammatory Profile Associated with Non-HLA Antibodies to G-Protein Coupled Receptors in Pediatric Kidney Transplant Recipients
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Background: The inflammatory profiles associated with non-HLA antibodies to G-protein coupled receptors in kidney transplant recipients (KTRs) are unknown.

We have recently shown that angiotensin II type 1 receptor antibody (AT1R-Ab) and Endothelin-1 Type A receptor antibody (ETAR-Ab) are prevalent and associated with poor clinical outcomes and elevations in TNF-α, IL-1β, IL-8, IFN-γ, IL-17, and IL-6 in pediatric KTRs. We aimed to expand this analysis by examining the association between these non-HLA antibodies and a broad panel of inflammatory markers in a different cohort of pediatric KTRs.

Methods: 153 rejections consisted of 50 clinical and 103 subclinical rejection cases. Among 406 non-rejection cases, 81 cases had an acute elevation of creatinine, and 325 cases had stable kidney function. For binary analysis, ETAR-Ab and AT1R-Ab were considered as positive for binary analysis. We calculated the area under the receiver operating characteristic (AUROC) for each test and the combination of both tests. We conducted a logistic regression to assess the performance of combined GEP and dd-cfDNA scores as continuous variables.

Results: Combining the GEP and dd-cfDNA can improve the ability to monitor allograft rejection. ETAR-Ab and AT1R-Ab are prevalent and associated with non-HLA antibodies and with poor outcome after transplant but are associated with tolerant kidney transplant recipients. Combining the GEP and dd-cfDNA can improve the ability to monitor allograft rejection. B cells have been associated with acute and chronic antibody mediated rejection and with poor outcome after transplant but are associated with tolerant kidney transplant recipients. Combining the GEP and dd-cfDNA can improve the ability to monitor allograft rejection.

Conclusions: AT1R-Ab and ETAR-Ab positivity is associated with a distinct inflammatory profile in pediatric KTRs in the first 2 years post-transplant. This distinct profile may help inform mechanistic studies and potentially identify new therapeutic targets to treat non-HLA associated allograft injury.

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PO2183

Immunoglobulin G (IgG) Glycosylation, Renal Function, and Anti-body-Mediated Rejection in Renal Transplant

Clara Barrios, Dolores Redondo-Pachón, Maria Jose Perez saez, Adriana Sierra Ochoa, Carlos E. Arias, Carla Burbuja, Anna Buxeda, Julio Pascual, Marta Crespo. Consorci Parc de Salut MAR de Barcelona, Barcelona, Spain.

Background: IgG glycome composition is a key regulator of immune system modulating inflammation at multiple levels. It has been associated to aging, infections response, autoimmune diseases or early kidney failure. Its role in KT has not been studied. Our aim was to analyze the prognostic and diagnostic value of IgG glycans in renal function after 1year of KT and in antibody-mediated rejection (AMR)

Methods: We analyzed 24 essential IgG glycans by High-performance Liquid Chromatography grouped them by biological function, according to the proportion of Galactosylated, Agalactosylated, Sialicylated, Fucosylated and Bisecting-GlcNAc structures. We measured baseline IgG glycans and one year after KT in 248 recipients (62%M:38%M) of 55.9±13.6 years, 36 with AMR. Association models were adjusted by donor characteristics, baseline renal function, age/sex, BMI, ATN-postKT and comorbidities

Results: Differences between IgG glycans at baseline and 1year values were associated with the achieved renal function: Higher Sialization (Coef [95% CI] 2.07 [0.23-0.99]) and Galactosylation (1.84 [0.0-3.6]) the better renal function and higher proportion of agalactosylated glycans associated worse renal function -2.02 [-4.1 - -0.34]. AMR occurred more frequently in patients with a higher proportion of Agalactosylated glycans (OR [95% CI]) 1.7 [1.15-2.51] and less in those with a greater proportion of Galactosylates 0.59 [0.4-0.87], Sialicylates 0.67 [0.45-0.9] and Bisecting-GlcNAc 0.66 [0.45-0.99] (figure)

Conclusions: Glycans, that modulate the IgG function, are a potential prognostic tool for renal function in KT and as a diagnostic support in the identification of patients who develop AMR.

PO2184

A Possible Effect of Glucagon-Like Peptide 1 Receptor Enhancement on Graft Kidney Function


Background: Successful kidney transplantation (KTX) has revolutionary improved comorbidities related to diabetic kidney disease in type 2 diabetic patients. Enormous evidence has accumulated that incretin enhancer, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have potential to boost native kidney function. However, little is known about a possible protective effect of its use on graft kidney function.

Methods: We conducted an observational cohort study to investigate the association between the use of GLP-1RA versus other antidiabetic medications (Non-GLP-1RA), and the 4-year risk of sustained eGFR decline (4 straight month-40% decrease from baseline) in consecutive kidney transplant recipients (KTRs) with type 2 diabetes who underwent KTX in our center from January 2012 through December 2018. Included were all KTRs with type 2 diabetes who were followed forward in time from month 1 post-transplant for 24 months or longer at the time of December 31, 2020. We calculated the propensity score of initiating GLP-1RA versus Non-GLP-1RA as a function of baseline covariates using logistic regression. Inverse probability of treatment weighting was generated from the propensity score and treatment-weighted odds ratio was estimated between the two treatment groups to better control for baseline confounding variables including presence or absence of protocol biopsy-proven interstitial fibrosis/tubular atrophy 1 month after KTX. Sodium-glucose cotransporter 2 inhibitors medication was treated as competing event.

Results: Seventy three were identified as GLP-1RAs users, 73 were on Non-GLP-1RA medications, and no deaths with graft function were observed during the study period. There were 6 sustained eGFR decliners in Non-GLP-1RA group whereas 1 in GLP-1RA group. According to multivariate analysis, GLP-1RA use after KTX was associated with a lower risk of sustained eGFR reduction (weighted odds ratio, 0.105; 95% confidence interval, 0.012-0.961).

Conclusions: GLP-1RA initiation and continuous use had a lower eGFR decline compared with other antidiabetic medications and may contribute to better kidney graft survival after KTX.

PO2185

Impact of Low-Normal vs. High-Normal Baseline Donor-Derived Cell-Free DNA Levels on Two-Year Allograft Function Following Kidney Transplantation

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Background: Donor derived cell free DNA (dd-cfDNA) is a biomarker that helps to predict acute rejection in kidney allografts. Baseline dd-cfDNA levels are <1% in 96% of kidney transplant recipients (KTRs) and a value ≥1% suggests allograft injury in the 1st month from acute rejection. dd-cfDNA levels <1% are considered as normal. We tested whether low-normal vs. high-normal baseline dd-cfDNA values would have differing impact on longitudinal allograft function.

Methods: We identified patients who underwent kidney transplantation at our center between September 2017 and June 2020 and had dd-cfDNA (AlloSure, CareDx, Brisbane, CA) levels under the surveillance protocol at or around 8 weeks post-transplantation. Those KTRs with dd-cfDNA levels ≤1.0% were included in the analysis. Patients were divided into 2 groups based on the dd-cfDNA levels: group 1 with dd-cfDNA <0.5% (low-normal) and group 2 with dd-cfDNA 0.5-0.99% (high-normal). Estimated glomerular filtration rates (eGFR) between the groups at 3 month intervals were compared using box plots and longitudinal eGFR up to 2 years post-transplant were compared between the groups using linear mixed model.

Results: There were 111 patients included in the analysis including 62 males and 49 females. Among the study group, 39 had living and 72 received deceased donor kidneys. There were 96 patients in group 1, and 15 patients in group 2. We observed no differences either in 3-month interval cross-sectional eGFRs (fig 1A) or 2-year longitudinal eGFRs (fig 1B) between the groups.

Conclusions: Our analysis found no differences between early post-transplant low-normal and high-normal baseline dd-cfDNA levels in terms of the impact on eGFR up to 2 post-transplant years in KTRs. These findings support the use of 1% cut off as a threshold to separate normal from abnormal dd-cfDNA levels.

Funding: Commercial Support - CareDx

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO2186
Baseline Trends in Tacrolimus Intrapatient Variability in Pediatric Kidney Transplant Patients
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Background: High tacrolimus intrapatient variability (IPV) is a known risk factor for inferior graft outcomes in kidney transplant patients. Baseline trends in tacrolimus intrapatient variability have not been well-defined in pediatric kidney transplant patients.

Methods: Pediatric patients who received a kidney-only transplant from 2010-2018 at a single center were considered for inclusion. Patients with follow-up time of at least 1 year were included. Tacrolimus IPV was determined using the mean coefficient of variation over the immediate 6-month time period prior to each tacrolimus level at each year post-transplant. All available tacrolimus levels were included in the analysis. Patients were stratified by age at time of transplantation (ages 1-6, 7-12, 13-18 years). A paired t-test was performed to evaluate the IPV change with increasing time post-transplant, with a specific post-transplant year tested against the prior year for each age group.

Results: 220 pediatric kidney transplant patients met inclusion criteria. Median age was 12.8 years. 117 patients (53.2%) were male, and 54 (24.5%) underwent living donor kidney transplant. IPV trends varied by age group, but IPV was high for all groups during the first year. After the first year, IPV decreased over time for patients in the 1-6 years group while it increased for those in the 7-12 and 13-18 years groups (Figure 1).

Conclusions: Tacrolimus IPV patterns differ in pediatric kidney transplant patients based on age at time of transplantation. It is likely that in the youngest group of patients, factors other than nonadherence explain their initial prolonged high IPV. More research is needed to quantitate and better understand the factors influencing variability in children given the association between IPV and adverse graft outcomes.

Figure 1. Tacrolimus intrapatient variability (IPV) trends over time post-transplant for different age groups

PO2187
The Impact of Intrapatient Tacrolimus Trough Level Variability over 2 Years Post Transplant on the Long-Term Allograft Outcomes in Kidney Transplant Recipients
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Background: The current study aimed to determine the impact of tacrolimus (TAC) trough level (CV) intra-patient variability (IPV) over 2 years after kidney transplantation (KT) on allograft outcomes.

Methods: In total, 1,143 patients with low immunologic risk were enrolled. The time-weighted coefficient variability (TWCV) of TAC-C0 was calculated, and patients were divided into tertile groups (T1: <24.6%, T2: 24.6–33.7%, T3: ≥33.7%) according to TAC-C0-TWCV until post-transplant 1st year. Moreover, they were classified into the low/low, low/high, high/low, and high/high groups based on a TAC-C0-TWCV value of 33.7% during post-transplant 0–1st and 1st–2nd years. We compared the allograft outcomes among the three tertile and four TAC-C0-TWCV groups.

Results: The T3 group had the highest rate of death-censored allograft loss (DCGL), and T1 itself was an independent risk factor for DCGL (adjusted hazard ratio (HR) 1.853, P = 0.029). In addition, sustained TWCV ≥33.7% until 2 years after KT showed the highest risk for DCGL (HR 2.395, P = 0.013). Moreover, the changes in TWCV during the 1st–2nd post-transplant year significantly affect to DCGL occurrence (HR of low/high 2.086, P = 0.045, HR of high/low 1.813, P = 0.021). Patients with an average TAC-C0 of ≥5 ng/mL in the high/high group were at highest risk for DCGL as well.

Conclusions: In conclusion, TAC-IPV is an important factor that can significantly affect comprehensive allograft outcomes. TAC-IPV after 1st year of KT was also considered an important factor for allograft outcomes. Moreover, TAC-IPV can significantly affect allograft outcomes even with a high average TAC-C0.

PO2188
The Balance Between Memory and Regulatory Cell Populations in Kidney Transplant Recipients with Operational Tolerance

Background: Donor-reactive memory cells represent a barrier to long-term kidney graft survival. A better understanding of regulatory mechanisms that counterbalance alloreactive memory responses may help to identify patients with operational tolerance.

Methods: The prospective, bicentric BALANCE study investigated the equilibrium between memory T cell subsets and regulatory T or B cells (Tregs, Bregs) in peripheral blood of kidney transplant recipients with operational tolerance (N=83), chronic rejection (N=8), and different immunosuppressive treatment regimens (N=81). Patients on hemodialysis and healthy individuals served as controls (N=50). In addition, the expression of Treg- and Breg-associated molecule genes was analyzed.

Results: Patients with chronic rejection showed a disrupted memory T cell composition with a significantly increased frequency of circulating CD8+ terminally differentiated effector memory (TEMRA) T cells than in patients with operational tolerance, patients on hemodialysis, or healthy controls (P<0.001). Compared to all other transplant recipients, the lowest ratios between CD8+ TEMRA and naive or effector T cells and the highest frequency of Tregs and transitional Bregs were found in operationally tolerant patients (for all P<0.001). Consequently, operationally tolerant patients showed, as compared to all other transplant recipients with different immunosuppressive regimens, the lowest ratios between CD8+ TEMRA T cells and Tregs or Bregs (for both P<0.001). A specific peripheral blood transcription pattern was found in operationally tolerant patients with an increased expression of Breg- and Treg-associated genes CD22 and FoxP3 and a decreased FcyRIIA/FcRIIB transcript ratio (for all P<0.001, as compared to all other transplant recipients).

Conclusions: Monitoring the balance between circulating CD8+ TEMRA T cells and regulatory cell subsets and their transcripts may help to distinguish transplant recipients with operational tolerance from recipients at risk of graft loss.

PO2189
Steering of Immunosuppression by Virus-Specific T Cells After Pediatric Kidney Transplantation (KTs) in the Randomized Controlled IVIST Trial
Lars Pape, Thirud Ahlenstiel-Grunow. University Duisburg-Essen Medizinische Fakultät, Essen, Germany.

Background: Pharmacokinetic monitoring alone is insufficient to estimate the intensity of immunosuppression after KTs. Levels of virus-specific CD4 T cells (CD4Tvis) have been shown to identify overimmunosuppression. The IVIST trial has demonstrated that additional steering of immunosuppressive therapy by CD4Tvis levels is safe and reduces exposure to immunosuppressants with significantly lower trough levels but without increasing the risk of acute rejections.

Methods: In the randomized controlled IVIST trial, 64 pediatric KTx recipients were randomized 1:1 to a control group with trough level monitoring of immunosuppressants or to an intervention group with additional steering by CD4Tvis levels against adenovirus (ADV), cytomegalovirus (CMV) and herpes simplex virus (HSV). The immunosuppression consisted of cyclosporine A, everolimus and glucocorticoids. CD4Tvis were quantified by cytokine flow cytometry in 20 visits during the two-year study period. In the intervention group we have analyzed the CD4Tvis levels and the number of Tvis-based dose adjustments of immunosuppressants.
Results: At time of transplantation, ADV-CD4Tvis were detectable in 20/31 patients (immunosuppression group), CVN-CD4Tvis and BCN-CD4Tvis only in 12/31. No significant ADV- or HSV-DNAemia was found; only two patients showed transient CMV-DNAemia at 4-12 hours, 48-72 hours and 72-96 hours post-transplant. SCr was measured just prior to transplantation, at 670 hours (IQR, 4.6-31.2) months after KTx. Serum and urine BKV DNA were measured by real-time PCR at baseline, 1 and 3 months after detection of BKV viremia/viruria. Lymphocyte profile and CD4(+)CD25(+)FoxP3(+) Tregs were measured by flow cytometry concurrently at these time points. Graft outcomes over 8 years were examined in relation to BK viremia, viruria levels, and lymphocyte profiles.

Conclusion: Tregs may play a role in BKV infection, reduction in the overall amount of immunosuppression is associated with improvement of BKV viremia/viruria and may lead to prevention or treatment of established AKI. The product of two novel biomarkers of cell cycle arrest, tissue Inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein (IGFBP-7) have shown promise in predicting AKI. In prior studies, TIMP-2/IGFBP-7 <0.3 had high negative predictive value and >2 high positive predictive value for AKI. Aims - 1) Investigate the early diagnostic value of TIMP-2/IGFBP-7 for DGF; 2) Correlate TIMP-2/IGFBP-7 with long term graft function. Methods: We enrolled 144 KT recipients with stable graft function between 1989 and 2018. Differentiation and expansion of Tregs were studied by flow cytometry to compare the Tregs subpopulations. Tregs were defined as CD4(+)CD25(+)FoxP3(+) cells.

PO2192
Diagnosis of Early Delayed Graft Function (DGF) using TIMP-2/IGFBP-7 Product in Transplant Recipients: Preliminary Results
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Background: DGF is acute kidney injury (AKI) defined as need for dialysis within one week of renal transplant. AKI is defined by a change in serum creatinine (SCr), however early recognition is limited by delay in creatinine rise. Accurate early biomarkers may lead to prevention or treatment of established AKI. The product of two novel biomarkers of cell cycle arrest, tissue Inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein (IGFBP-7) have shown promise in predicting AKI. In prior studies, TIMP-2/IGFBP-7 <0.3 had high negative predictive value and >2 high positive predictive value for AKI. Aims - 1) Investigate the early diagnostic value of TIMP-2/IGFBP-7 for DGF; 2) Correlate TIMP-2/IGFBP-7 with long term graft function. Methods: This is a prospective, double-blinded single-center observational study with post-enrollment of 150 transplant recipients. Urine TIMP-2/IGFBP-7 was measured in (ng/mL)/1000 with a commercial kit, Nephrocheck (Astute Medical, San Diego, CA) at 4-12 hours, 48-72 hours and 72-96 hours post-transplant. SCr was measured just prior to transplant, 1 week post-transplant, and at 1, 3, 6, 9 and 12 months post-transplant.

Regulatory T cell subpopulation according to the patient’s characteristics.
Results: Thus far, 64 patient samples have been collected, 11 with DGF. Mean TIMP-2*IGFBP-7 were 3.08 ± 0.63 vs 0.54 ± 0.23 (p-value <0.001) at 4-12 hours, 3.39 ± 0.93 vs 0.38 ± 0.13 at 24-48 hours (p-value <0.001), and 1.73 ± 0.76 vs 0.62 ± 0.27 (p-value <0.09) at 72-96 hours in DGF vs non DGF patients respectively. Mean Scr at 1 week were 6.14 ± 0.71 mg/dL in DGF vs 2.13 ± 0.26 mg/dL (p-value <0.001) in non-DGF. Correlation between peak TIMP-2*IGFBP-7 at 24-48 hours and Scr at 1, 3, 6, 9, and 12 months, was nonsignificant.

Conclusions: These preliminary results confirm the use of TIMP-2*IGFBP product measured by Nephrocheck in the diagnosis and prediction of DGF in the post-kidney transplant period as early as 4-12 hours, and peaking at 24-48 hours. The non-DGF TIMP-2*IGFBP-7 means were higher than prior reports, suggesting mild renal injury in the peritransplant period in those patients without DGF. The current sample size is too small and underpowered as of yet to draw conclusions on prediction of long-term renal dysfunction.

Funding: Commercial Support - Astute Medical Inc

PO2193
Kidney Injury in Hematopoietic Stem Cell Transplant (HCT) Recipients: Transcriptome Profiling and Development of Urinary Biomarkers
Elly Varna, Thalia Salinas, Carol Y. Li, Catherine Snopkowski, Thangamani Muthukumar. Weill Cornell Medicine, New York, NY.

Background: In kidney biopsies of HCT recipients, thrombotic microangiopathy with/tubulointerstitial/macromolecular vascular inflammation suggest the possibility of kidney being a target of graft versus host disease. We tested the hypothesis: (i) kidney inflammation/injury in HCT recipients is immune mediated, (ii) urinary mRNA profile may be used as a noninvasive biomarker.

Methods: (i) RNA-sequencing of native kidney from 6 HCT recipients with kidney injury was performed. We compared the transcriptome profile to that of allograft kidney. (ii) Urine samples from 9 HCT recipients were collected. We calculated the CTOT-04 signature score for each recipient. We compared the score to that of kidney allograft recipients.

Results: Of the 4188 genes (26% of 16375) that were different (FDR-P<0.05) between HCT and Normal, 2152 were shared among HCT, ACR, and AMR; 1442 were unique to HCT (Figure 1). Shared genes revealed enrichment of innate and adaptive immune system pathways. Urinary cell CTOT-04 signature score was higher in AKI/renal failure and interstitial inflammation in the native kidney and resembled ACR of kidney allograft recipients (Figure 2).

Conclusions: In recipients of HCT: (i) kidney inflammation/injury is immune mediated, (ii) urinary cell mRNA profiling is useful for diagnosing kidney injury.

PO2194
The Role of Hyperleptinaemia and Low Values of Interleukin 10 in De Novo Donor-Specific Antibody Production After Kidney Transplantation
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Background: White adipose tissue secretes a number of peptide hormones, including leptin, adiponectin, and several cytokines. The aim of this paper was to determine the role of selected adipocytokines (leptin and adiponectin) and interleukins (IL-10 and IL-6) on the development of graft rejection in protocol biopsy after kidney transplantation.

Methods: In a prospective analysis (n=104), we monitored the values of leptin, adiponectin, IL-6, and IL-10 prior to the transplantation and in the 3rd month after the transplantation. The protocol biopsy of the graft was performed in the 3rd month after the transplantation. The group was divided into the following according to the biopsy result: negative result, IFTA 1, borderline, and DSA positive.

Results: After adjusting for the differences in the baseline recipient and donor characteristics, we identified the hyperleptinaemia baseline (HR=2.0444, P=0.0341) and month 3 (HR=49.8043, P=0.0001) as independent risk factors for de novo DSA positivity. A low value of IL-10 month 3 is a risk factor for de novo DSA positivity (HR=3.0746, P=0.0388).

Conclusions: Higher leptin levels might play a role in rejection and de novo DSA production. We also confirmed the influence of low values of IL-10 on the development of de novo DSA. We assume that values of adipocytokines in context of other risk factors can predict the immunological risk of patients after kidney transplantation.

Funding: Government Support - Non-U.S.

PO2195
Diagnostic Performance of Donor-Derived Cell-Free DNA Assay (AlloSure®) in Kidney Transplant Recipients with Graft Dysfunction: A Single-Center Study
Muhammad S. Nasir, Ayush Singh, Neeraj Singh. Willis Knighton Medical Center, Shreveport, LA.

Background: Circulating donor-derived cell-free DNA (dd-cf-DNA) is a non-invasive biomarker of kidney allograft injury with a high negative predictive value for ruling out active rejection in patients with evidence of graft dysfunction. At our center, we
compared the AlloSure® test (CareDx®) for the dd-cfDNA assays using >1% as the cut-off value suggested by the DART study or an increase of >30% from the previous value against the gold standard biopsy results and calculated its performance metrics.

Methods: From Dec 2019 to Oct 2020, we found 16 patients who had their 21 AlloSure® assays drawn which were within 4 weeks of for-come biopsy sampling. In assessment of this cause of 21 samples, 17 had HLA, 5 had proteinuria, and 3 had clinical symptoms of volume overload.

Results: AlloSure® and biopsy results were concordant in 14/21 (66.7%) samples. Of the 21 for-come biopsies, 8 biopsies were positive for rejection (2 borderline, 1 TCGR, 1 mixed AMR/TCMR, 1 chronic). AlloSure® was positive in 2 of these 8 rejections (1 TCGR, 1 mixed AMR/TCMR). However, it was false-negative in the other 6 rejections (2 borderline, 3 AMR, 1 chronic). Out of the 13 negative biopsy results, AlloSure® was negative in 12 samples and false-positive in one sample. The performance metrics of the patient’s results: sensitivity 92.3%, positive and negative predictive values of 66.7%, and accuracy of 66.7%.

Conclusions: Although we had a sample size, it can be concluded from this study that AlloSure® has a high specificity to diagnose active graft rejection in kidney transplant recipients.

Table 1: 2 x 2 Table

PO2197

Can Donor-Derived Cell-Free DNA or Gene Expression Profile Be Used to Monitor Response to Treatment After Subclinical Acute Rejection? Sookhyeon Park, Zachary Dietch, Kexin Guo, Lihui Zhao, John J. Friedewald. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Subclinical acute rejection (subAR) is defined as acute rejection with stable kidney allograft function. Creatinine is not sensitive enough to detect subAR. Donor-derived cell-free DNA (dd-cfDNA) and gene expression profile (GEP) have been used for acute rejection detection in kidney allograft. We hypothesized that dd-cfDNA and GEP could be used to monitor response to treatment of rejection after subAR.

Methods: We analyzed dd-cfDNA and GEP results from 14 unique subjects in the CTOT08 study with subAR who had 8 weeks follow-up biopsy after treatment. Blood samples were paired with kidney biopsies, and collected after subAR during the intensive monitoring periods. We calculated the mean and standard deviation (SD) for each group at the same time points. A paired T-test was used to generate p-values. We conducted locally estimated scatterplot smoothing (LOESS) and linear mixed effect models for the analysis of serial changes of dd-cfDNA scores.

Results: Of 14 patients, subAR resolved in 5 patients (36%) but 9 (64%) patients had persistent rejection after treatment. The slope of dd-cfDNA A scores was not significantly different between the resolved and the unresolved group (p-value = 0.43) (Figure 1A). The slope of GEP scores in the resolved group tended to be steeper than unresolved group one after treatment but was not statistically significant between the two slopes (p-value = 0.06) (Figure 1B).

Conclusions: GEP scores showed a greater decrease after successful treatment compared to dd-cfDNA scores. Repeating GEP after subAR might be useful to monitor treatment of rejection.

Funding: Commercial Support - Viracor-Eurofins

PO2198

Immunosuppression Could Influence De novo Angiotensin II Type 1 Receptor Antibodies Development Early After Kidney Transplantation Bogdan M. Sorohan,1,2 Andrea Ioana Berechet,2 Cristina Bucsa,2 Corina Tinca,3 Bogdan Obrica,1,2 Gerem Ismail.1,2 Universitatea de Medicina si Farmacie Carol Davila, Bucharest, Romania; 3Institutul Clinic Fundeni, Bucharest, Romania.

Background: Angiotensin II type 1 receptor antibodies (AT1R-Ab) are non-HLA autoAb associated with graft rejection and detrimental effects on graft function in kidney transplantation (KT). Nevertheless, the data regarding risk factors associated with AT1R-Ab development is scarce. To our knowledge, immunosuppression (IS) has not yet been reported as a potential risk factor. We sought to evaluate the incidence of de novo AT1R-Ab at year 1 after KT and risk factors associated with their formation.

Methods: We performed a prospective study on 58 KT recipients, transplanted between October 2018 and October 2019, who were followed for 1 year. Exclusion criteria: age <18 years and preformed AT1R-Ab. AT1R-Ab were evaluated at 1 year after KT using an ELISA technique and the cut-off value for detection was ≥10 U/ml. Logistic regression analysis was used to identify risk factors associated with AT1R-Ab formation.

Results: Twelve out of 58 patients (20.6%) had de novo AT1R-Ab at 1 year of follow-up. Mean age of the study cohort was 40.8±10.5 years, 60.3% were males and 17.2% had a preemptive KT. Glomerular diseases was the main cause for CKD (27.6%). Donors mean age was 46.6±15.6 years, 62.1% were cadaveric donors and 31% of patients had ≥4 mismatches. Monoclonal Ab directed against IL-2 receptor (84.5%) was the main induction IS used. Immediate-release tacrolimus (TAC) was used in 53.4% and mycophenolate sodium was preferred in 89.7% of cases. Patients with de novo AT1R-Ab had a significantly decreased BMI (21.4±2.9 kg/m²) compared to the baseline value of 23.0±2.3 kg/m² (p=0.04). Blood urea nitrogen (BUN) and creatinine (Cr) were significantly lower in the patients with de novo AT1R-Ab compared to the others (BUN: 48.6±30.9 mg/dL vs 81.5±33.7 mg/dL, p=0.01 and Cr: 1.5±0.7 mg/dL vs 2.1±0.9 mg/dL, p=0.04). A total of 12 cases (20.6%) of AT1R-Ab were reported at 1 year of follow-up. We performed logistic regression analysis to identify risk factors associated with AT1R-Ab formation.

Conclusions: The incidence of de novo AT1R-Ab was 20.6% and rTAC induction IS was an independent risk factor for de novo AT1R-Ab development (OR= 5.62; 95%CI: 1.11- 28.34, p=0.03) and immediate-release TAC had a trend of association with Ab (OR= 5.02; 95%CI: 0.93- 27.06, p=0.03) at 1 year after KT.

Conclusions: The incidence of de novo AT1R-Ab was 20.6% and rTAC induction IS was an independent risk factor for de novo AT1R-Ab development. Our results suggest that IS could influence de novo AT1R-Ab formation.

PO2199

The Histological Fingerprint of Kidney from High Kidney Donor Profile Index Diabetic Donors Transplanted in Non-Diabetic Recipients Giorgia Comai, Valeria Corradetti, Federica Maritati, Claudia Bini, Marco Busutti, Gaetano La Manna. Nephrology, Dialysis and Kidney Transplantation Unit, IRCCS Azienda Ospedaliera-Universitaria di Bologna, Bologna, Italy.

Background: To face the persistent organ shortage and the increasing age and comorbidities of donors, criteria to donation have been expanded. Diabetic donors are recognized as a reliable source of organ, few data are available on the histological evolution of these organs for these reasons we compare the pre implantation biopsy of high-KDPI diabetic donor with a protocol biopsy of non diabetic recipients.

Methods: We performed a retrospective analysis of deceased donors from 2004 to 2015. We selected those with a diagnosis of diabetes and with available pre implantation kidney biopsy (10) that was scored for diabetic and Karpinski score. Then we selected those recipients whose at time of analysis (T1) were still on follow up, had not a history of diabetes and executed at least one biopsy which has been compared with the previous one.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO2201

Donor-Derived Leukocyte Chemotactic Factor 2 Amyloidosis in Renal Allografts

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Introduction: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a relatively common form of amyloidosis with strong ethnic predilection in the Hispanic population. Patients tend to be older and present with chronic kidney disease with variable proteinuria. Histologically, ALECT2 has a unique preference for interstitial amyloid positive for ALECT2 on immunohistochemistry and mass spectroscopy. Case Description: Case 1: 69-year-old (yo) Hispanic man with type II diabetes and end-stage renal disease (ESRD) received an 86% Kidney Donor Profile Index (KDPI) deceased donor renal transplant (DDRT) from a 52-yy Hispanic woman who died of a stroke. The recipient had delayed graft function and suboptimal nadir serum creatinine (SCr) of 2.6 mg/dl. Proteinuria initially peaked at 2.3 g/g, which decreased to <1 g/g at 4-mo post-transplant (tx). Both time-zero and 3-mo protocol biopsies (bx) revealed widespread interstitial amyloid positive for ALECT2 on immunohistochemistry and mass spectroscopy. Case 2: 45-yy Hispanic female with ESRD of unknown etiology received a 78% KDPI DDRT from a 60-year-old female with no medical history who died from head trauma. The recipient experienced immediate graft function with new baseline SCr of 1.2-1.6 mg/dl. She had persistent proteinuria following tx and underwent bx at 2-, 3-, and 6-mo post-tx. The bx showed mostly interstitial amyloid, later confirmed to be ALECT2. Additionally, the patient developed focal segmental glomerulosclerosis (FSGS) as well as CKD infection of the allograft. She eventually lost her graft ~2 years post-tx, likely from FSGS rather than ALECT2.

Discussion: Rare cases of donor-derived ALECT2 have been reported in the literature and suggest that kidney allografts with limited and localized donor-derived ALECT2 involving <10% of the renal parenchyma have good outcomes. Our cases represent more severely affected donor kidneys. Although the clinical course for our patients were suboptimal, other factors aside from ALECT2 were likely the major contributing factors. Thus, donor-derived ALECT2 is likely of low consequence in the recipient allograft.

PO2200

Utility of Noninvasive Rejection Biomarkers to Assess the Risk of Rejection in Kidney Transplant Recipients with Post COVID-19 Infection

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Introduction: COVID-19 infection is associated with 25% mortality in kidney transplant recipients (KTRs). Treatment of Coronavirus Disease 2019 (COVID-19) infection in KTRs has involved reduction of immunosuppressants (IS). This potentially increases the risk of allograft rejection in the setting of reduced immunosuppression. We reported 6 cases of kidney allograft rejection post COVID infection

Case Description: Total 123 kidney transplant recipients had COVID-19 infection between March 2020 and February 2021. Immunosuppression was reduced routinely in patients who had symptomatic COVID-19 infection. We implemented the protocol of screening tests to assess for rejection which included dd-cfDNA, gene expression profile (TruGraf), donor specific antibody (DSA). Elevated serum creatinine greater than 25% over baseline, dd-cfDNA value greater than 1%, TruGraf value of Non-TX (NT) or up-trending DSA prompted to allograft biopsy to rule out rejection.

Discussion: Twelve patients out of 123 KTRs received kidney biopsy for above mentioned indications Only 4.8% had kidney rejection (6 out of 123 patients): 3 patients with acute cellular rejection (ACR) Banff IIB rejection, 2 patients with borderline ACR, and 1 patient with antibody mediated rejection (AMR). Of these 6 patients with rejection 5 patients have elevated dd-cfDNA peri COVID infection, 3 patients with elevated Cr and 1 patient had Non-Tx. Three patients with rejection were transplanted within 1 year. The patients with Banff IIB rejection were treated with anti-thymocyte globulin (ATG) and 1 patient with AMR due to AT1R antibody was treated with methylprednisolone, IV Ig and Losartan. Only 4.8% had kidney rejection post COVID infection. Despite reduction in IS, COVID infection did not increase the risk of allograft rejection and can monitor the risk of rejection by using non-invasive rejection biomarkers.
Autoimmune Encephalitis with Concurrent Epstein-Barr Virus Infection in a Renal Transplant Patient

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Introduction: Epstein-Barr virus (EBV) infection following renal transplant is typically associated with post-transplant lymphoproliferative disorder (PTLD). Autoimmune encephalitis is caused by antibodies against N-methyl-D-aspartate receptor (NMDAR), a ligand-gated ion channel with a crucial role in synaptic transmission. We describe a patient who developed encephalitis 1 year after renal transplant with cerebral spinal fluid (CSF) analysis positive for NMDAR antibodies and evidence of EBV infection on brain biopsy without PTLD or malignant processes. To our knowledge, this is the 1st case with tissue evidence of EBV infection on brain biopsy in renal transplant.

Case Description: A 70-year-old female with end stage renal disease from Type 2 Diabetes mellitus who received a deceased donor renal transplant one-year prior was admitted for 3 weeks of progressively worsening mentation. Immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Brain MRI did not reveal any acute findings. EEG showed generalized slowing consistent with diffuse encephalopathy. CSF analysis showed lymphocytic pleocytosis and elevated protein level. The infectious workup was negative except for positive EBV PCR in CSF. Cytometry did not reveal any evidence of PTLD. CSF autoimmune panel demonstrated NMDAR antibody. Brain biopsy showed a chronic inflammatory process with features of EBV infection. EBV-infected cells were detected in tissue specimen via in-situ hybridization with EBV-encoded small RNA. Patient initially received ganciclovir, abicicline, and broad-spectrum antibiotics. Treatment then changed to steroids, IVIG and plasmapheresis for autoimmune encephalitis, all of which were stopped and ganciclovir was restarted when brain biopsy was positive for EBV. Unfortunately, patient did not show any clinical improvement possibly due to delayed diagnosis and went home with hospice care.

Discussion: EBV Encephalitis without PTLD following renal transplant is uncommon. Only a few cases have described renal transplant patients with encephalitis and antibody findings of NMDAR antibodies and EBV DNA in CSF. The relationship between EBV infection and AE remains unclear; however, EBV infection may play a role in the pathogenicity of NMDAR antibodies. AE can occur in the setting of chronic immunosuppression and should not be overlooked to avoid delay in diagnosis and treatment.
Discussion: This is a rare case of bilateral pyomyositis in a kidney transplant patient. The inability to culture an organism is likely due to preceding IV antibiotic treatment. This case underscores the importance of keeping a broad differential diagnosis and obtaining a detailed history when treating immunosuppressed patients.

Figure 1

PO2207

Dihydroxyadenine Crystals Leading to Renal Graft Loss

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Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive disease which leads to excessive production and renal excretion of poorly soluble 2,8-dihydroxyadenine (DHA). This causes crystal-induced acute kidney injury and progressive chronic kidney disease (CKD). We describe a case of DHA nephropathy in a renal transplant recipient leading to graft failure.

Case Description: A 69 year old female with ESRD secondary to recurrent nephrolithiasis underwent a deceased donor kidney transplant. The stone composition was previously unknown but she underwent genetic testing and was found to be homozgyous for APRT c.81-3C>G mutation which was reported as a variant of uncertain significance. APRT activity level was checked and was within normal range. As a result, allopurinol was stopped. Her serum creatinine which was 1.6 mg/dl started to gradually increase to 5.5 mg/dL. She underwent a kidney biopsy which showed extensive tubular cytoplasmic DHA deposition. Despite restarting allopurinol, renal function continued to worsen and she developed uremic symptoms. She was initiated on hemodialysis.

Discussion: APRT deficiency is a rare condition and novel mutations are being reported. It is likely that the mutation of unknown significance which our patient has might be another novel mutation associated with APRT deficiency. DHA stone formation can occur even when APRT levels are normal or detectable. It is of utmost importance to continue allopurinol in patients with known DHA stones as genetic testing and APRT level may be misleading and stopping allopurinol will result in irreversible kidney damage enabling prompt therapy with resolution of the symptoms and hypercalcemia.

Figure 1

PO2208

Hypercalcemia in Immunocompromised Host: Beware of Zebras


Introduction: Hypercalcemia has varied etiology with treatment dictated by underlying cause. We present an immunocompromised host with weight loss, lymphadenopathy and hypercalcemia masquerading as malignancy.

Case Description: A 74 year old male construction worker with deceased donor liver transplant 4 months earlier on tacrolimus/mycophenolic acid (MPA) maintenance and stage 4 chronic kidney disease presented with constitutional symptoms and 20 pound weight loss. Serum creatinine was 2.5 mg/dl and corrected calcium 11.9 mg/dl. CT scan showed mediastinal and bilateral axillary lymphadenopathy. Serum EBV and CMV PCR were negative. Work up for hypercalcemia revealed: intact PTH 6.8 picogram/ml (11.0-68.0), 25 OH vitamin D 44.6 ng/ml (30-100), iCa ratio 1.45 (0.26-1.65) and absent M-spike on serum protein electrophoresis. Blood culture grew Cryptococcus neoformans and serum Cryptococcal antigen titer was positive at 1:4067. Lumbar puncture revealed CSF lymphocytic pleocytosis and positive cryptococcal antigen titer at 1:32. Axillary lymph node biopsy showed cryptococcal lymphadenitis with diffuse involvement by encapsulated yeast forms within non-necrotizing granulomatous inflammation (fig 1). Patient was started on induction treatment with intravenous liposomal amphotericin B and oral fluconazole till 2 weeks after negative blood cultures followed by 8 weeks of consolidative therapy with oral fluconazole. MPA was stopped and tacrolimus continued. Hypercalcemia resolved a week after initiating antifungal therapy. Patient doing well 4 months later on maintenance fluconazole.

Discussion: Hypercalcemia is a rare manifestation of disseminated fungal infection. The exact etiology is unclear but 1, 25 di (OH) vitamin D and PTHrp are implicated. Weight loss and lymphadenopathy in our immunosuppressed patient raised concern for malignancy. However, blood culture and lymph node histology clinched the diagnosis enabling prompt therapy with resolution of the symptoms and hypercalcemia.

Figure 1

PO2209

A Rare Case of Collapsing Focal Segmental Glomerulosclerosis Caused by Cytomegalovirus in a Renal Transplant Recipient

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Introduction: Cytomegalovirus (CMV) is a DNA virus that is associated with several clinical manifestations in renal transplant recipients (RTR), presenting often with asymptomatic viremia, CMV syndrome, and tissue invasive disease in the lungs, colon,
Use of Lipoprotein Apheresis in Recurrent Focal Segmental Glomerulosclerosis Following Transplant
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Introduction: Primary focal segmental glomerulosclerosis (FSGS) recurs in 20-50% of transplanted kidneys and has a high rate of transplant failure. We report a case of recurrent FSGS treated with lipoprotein apheresis (LDL-A).

Case Description: A 27-year-old male with primary FSGS underwent a DBD kidney transplant. He was ESRD on PD and anuric. ATG and steroids were given for induction. On post-op day (POD) 2, his spot urine protein was >2000 mg (unable to calculate urine protein/creatinine ratio (UPCR)). Serum creatinine was 1.47 mg/dL (pre-transplant: 9.65 mg/dL). With concern for recurrent FSGS, emergent therapeutic plasma exchange (TPE) and losartan were started. On POD 3 and 4, proteinuria was >2000 mg: TPE was done daily and adrenocorticotropic hormone (ACTH) and rituximab started. Despite 5 days of TPE and medical therapy, proteinuria was >2000 mg. On POD 8, LDL-A was started. Prior to second LDL-A run, his proteinuria was 1990 mg but 294 mg afterwards. Proteinuria rebounded between treatments, but steadily decreased: by week 3, UPCR was 686 mg/g and by final LDL-A, was 200 mg/g. Renal function was stable and biopsy had no podocyte effacement. He completed LDL-A biweekly for 3 weeks, then weekly for 6 weeks. ACTH and rituximab were continued. Currently, his UPCR is 9 mg/g.

Discussion: Treatment of recurrent FSGS centers on plasma exchange and immunosuppression. By lowering LDL levels, LDL-A is thought to reduce proteinuria by reducing vascular permeability and improving response to immunosuppressive agents. Case reports indicate efficacy, but currently the use of LDL-A is designated as a humanitarian device exemption for drug resistant recurrent FSGS in transplanted kidneys by the FDA. Although this modality is uncommon, our case suggests that patients with recurrent FSGS may benefit from early initiation of LDL-A.

Iron Overload Syndrome and Primary Focal Segmental Glomerulosclerosis Recurrent with Monthly Plasma Exchange Therapy: Long-Term Second Kidney Allograft Survival
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Introduction: Patients who lose their allograft due to recurrent FSGS are usually not retransplanted since the risk of recurrence (80-100%). Proteinuria as a result of glomerular damage is linked to tubulointerstitial injury, which is associated with increased filtration of transferrin-bound iron and can lead to tubular accumulation.

Case Description: A 32-year-old female with a history of collapsing FSGS, living related kidney transplant with loss of the allograft function due to recurrent disease underwent a 2nd kidney transplantation in October 2018. At 2 months post transplantation elevated levels of proteinuria (6 g/g), kidney biopsy (KB) demonstrated recurrent FSGS. She received treatment with high-dose steroids, CsA and an intensive course of plasma exchanges (PEx) due to persistent proteinuria. There is no history of blood transfusions, iron treatment and diseases with ineffective erythropoiesis. Ferritin levels (15000 ng/ml) and a MRI with liver and spleen iron deposition pointed to the diagnosis of Hereditary Hemochromatosis (HH), common mutations (C282Y, H63D and G320V genes) were negative. KB of 2020 demonstrated iron deposition (ID) in tubular epithelial cells.

Discussion: Histological evidence of ID in the tubulointerstitium can be related to persistent proteinuria. The negative genetic testing is common in the Hispanic race in which there is a lesser prevalence for the most frequent mutation, C282Y homozygosity (0.03% compared to 0.44% in Whites). We assume that this patient has a genetically unknown type of HH. To our knowledge this is the first reported case in which an Iron Overload Syndrome (IOS) is associated with FSGS. PEx is a therapeutic option in patients with recurrent FSGS, also used in IOS.
Introduction: The high risk APOL1 genotype are associated with an increased risk of developing non-diabetic kidney disease. In the post-kidney transplant setting, a high-risk donor APOL1 genotype (but not recipient genotype) is associated with an increased risk of graft failure and proteinuria, indicating that it is local glomerular APOL1 gene expression that confers disease rather than systemic gene expression. Here, we present 2 patients that developed post-transplant focal segmental glomerulosclerosis (FSGS) after an initial diagnosis and treatment of Antibody-mediated rejection (AMR).

Case Description: Two patients with end stage kidney disease, highly sensitized, received deceased donor kidney transplants from African American donors (one in 2019 and the other a retransplant in 2020). Donors were without discernable proteinuria on urine dipstick. Initial post transplant courses were complicated by AMR treated as per center protocol. Tissue-based whole biopsy gene expression studies on kidney biopsy specimens (MMdx, using Molecular Microscope, Alberta, Canada) confirmed AMR along with grossly elevated interferon-γ gene expression. Subsequently each developed nephrotic range proteinuria with biopsy-confirmed FSGS and ongoing AMR. In both patients, in the absence of a prior history of FSGS and a delayed development of proteinuria in the first case (2019, patient 1), an absence of recurrence in the first allograft in the second case (2020, patient 2), a diagnosis of donor-derived APOL1 nephropathy was considered and retrospective donor genotyping revealed the intermediate G1/G0 genotype. See Figure for more details.

Discussion: We hypothesize that extreme local interferon-γ activation due to AMR was the primary trigger that could have resulted in local APOL1 gene activation and subsequent podocytopathy. Similar data was recently reported by Shetty et al, in a kidney transplant patient with COVID associated collapsing nephropathy and G1/G0 donor genotype. Based upon these data we hypothesize that the G1/G0 genotype may represent intermediate risk for podocytopathies. Further research is needed in this area to confirm these initial associations.

PO213
Early Recurrence of Fibrillary Glomerulonephritis After Kidney Transplantation
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Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerulonephritis characterized by glomerular Congo red negative nonbranching fibrils on electron microscopy (EM). The optimal treatment for FGN is unclear and the renal prognosis is poor, with up to half of patients progressing to end-stage kidney disease (ESKD) by four years. Kidney transplantation has a variable recurrence rate after transplant ranging from 9 to 50%.

Case Description: A 57-year-old male with a history of cirrhosis secondary to nonalcoholic fatty liver disease and ESKD secondary to FGN was hospitalized for acute kidney injury. The patient underwent simultaneous liver and kidney transplantation four weeks prior to presentation. The patient underwent induction with basiliximab and started on tacrolimus, mycophenolate mofetil, and prednisone for maintenance immunosuppression. The patient’s serum creatinine had increased from the previous nadir of 2.0 mg/dL to 2.7 mg/dL. Given worsening allograft function, a transplant kidney biopsy was performed. The patient’s biopsy showed evidence of recurrent fibrillary glomerulonephritis, including positive immunohistochemical staining for DNAJB9 and ultrastructural findings of mesangial nonbranching fibrils averaging 21.5 nm in diameter. The biopsy also showed acute tubular necrosis, secondary global and focal segmental glomerulosclerosis, and tubular atrophy and interstitial fibrosis in 20-30% of the cortex. There was no evidence of acute T-cell-mediated rejection or antibody-mediated rejection. The patient’s allograft function improved and ranged from 1.5 - 1.7 mg/dL at the time of discharge. The patient is now six months from transplant and has stable allograft function and minimal proteinuria.

Discussion: FGN recurrence after kidney transplantation has been described in case reports and case studies. In the most recent and largest study, utilizing DNAJB9 and protocolized post-transplant biopsy, the authors showed a recurrence rate of 21% and a median time to recurrence of 10.2 years. Additionally, all biopsies before five years were negative in their cohort. Allograft failure was seen in 35% of patients with recurrent FGN. To our knowledge, this case is the earliest reported recurrence of FGN after transplantation. In patients with a history of FGN, recurrent disease should be considered in the differential of early allograft dysfunction.

PO214
Donor-Derived Fibrillary Glomerulonephritis in a Renal Allograft

Introduction: Fibrillary glomerulonephritis (FGN) is a rare progressive renal disease that is defined by the presence of randomly oriented non-branching fibrils showing positive immunostaining for DnaJ homolog subfamily B member 9 (DNAJB9). Recurrent FGN in renal allografts have been described with an indolent course. We report a case of donor-derived FGN in a renal allograft.

Case Description: A 73-year-old female with history of end-stage renal disease (ESRD) due to anti-myeloperoxidase antibody-associated pauci-immune glomerulonephritis received a preemptive deceased donor renal transplant from a 62-year-old 79% Kidney Donor Profile Index female. The patient experienced slow graft function and nadir serum creatinine (Cr) of 1.7 mg/dL at 4 months post-transplant with subsequent Cr stabilizing in the 2.0-2.3 mg/dL range. Proteinuria mainly fluctuated between 1-2 g/g. Time-0 biopsy demonstrated mild mesangial widening/hypercellularity with rare nodules and kappas light chain-restriction, consistent with donor-derived FGN. 4-month surveillance biopsy showed similar findings. Background renal parenchyma showed moderate chronicity with prominent chronic vascular disease. At 10-months post-transplant, Cr remains at ~2 mg/dL and proteinuria remained in the 1-1.6 g/g range.

Discussion: FGN carries a poor prognosis with nearly half of patients progressing to ESRD within a few years. A case series of recurrent FGN after kidney transplantation suggests a relatively benign clinical course including a single report of donor-derived FGN (from a living related donor) without proteinuria in the recipient. Our case shows a more severely afflicted allograft that resulted in persistent low-grade but stable proteinuria in the recipient. Suboptimal Cr was also observed following transplant as well, although the allograft had other factors such as chronicity and chronic vascular disease.
**PO2215**

A De Novo Case of C1q Nephropathy in a Renal Allograft

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**Introduction:** C1q nephropathy (C1qN) is a rare idiopathic glomerulopathy that is characterized by mesangial C1q deposition in the absence of systemic lupus erythematosus or membranoproliferative glomerulonephritis. Clinical manifestations vary, but can include proteinuria, hematuria, and renal dysfunction. C1qN is not usually responsive to corticosteroids and outcomes are poor for most patients. We describe a de novo, but clinically silent case of C1qN in a renal allograft incidentally detected on surveillance biopsy.

**Case Description:** A 20 year old male, with history of end stage renal disease secondary to congenital renal hypoplasia, on maintenance tacrolimus, mycophenolate mofetil, and oral prednisone, underwent a surveillance biopsy 1 year after a deceased donor kidney transplantation. Laboratory studies revealed a baseline serum creatinine of 1.7 mg/dl and a spot urine protein to creatinine ratio of 258 mg/g. Urinalysis did not show hematuria and the rheumatologic workup was unremarkable. Light microscopy revealed minimal mesangial hypercellularity without endocapillary proliferation. Immunofluorescence microscopy demonstrated granular mesangial staining for C1q with positive staining for IgG, IgM, C3, C4, and kappa and lambda light chains. Electron microscopy revealed mesangial and paramesangial electron-dense immune deposits.

**Discussion:** Unlike other C1qN cases described in the literature, our patient did not have evidence of an underlying autoimmune disease or viral infection. Renal biopsy demonstrated positive immunofluorescence staining of IgG, IgM, C3, C4, and kappa and lambda light chains, in addition to C1q. Moreover, there was no evidence of proteinuria, hematuria, or renal dysfunction. One question that arises is whether this patient, with a history of congenital renal hypoplasia, was susceptible to developing an autoimmune process that was otherwise being masked by immunosuppression. This case emphasizes the following: (1) further research is needed to determine the frequency and length of monitoring of de novo C1qN in renal transplant recipients, and (2) further research is needed to determine the optimal therapeutic regimen.

**PO2216**

Repository Corticotropin (Acthar®) in Treating De Novo C3 Glomerulonephritis Post Transplantation

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**Introduction:** De novo C3 glomerulonephritis (C3GN) post-transplant is uncommon. Although eculizumab has been used successfully in several cases, the response is heterogeneous and treatment strategies remain undefined. The use of repository corticotropin in C3GN has not been described in the literature.

**Case Description:** A 48-year-old African American male with kidney transplantation secondary to diabetic nephropathy presented 6 years post-transplant with lower extremity edema and nephritic range proteinuria of 8.2 g/g of creatinine. His renal allograft biopsy confirmed the diagnosis of C3GN (Figure 1). He was treated with ecucilizumab (Solaris®) 900 mg IV once weekly for 4 weeks and repository corticotropin (H.P. Acthar® gel) 80 units subcutaneous twice weekly for 6 months with complete resolution of proteinuria within 3 months of the treatment. However, the patient presented again after 6 months of completing therapy with a recurrence of proteinuria which peaked at 11.6 g/g of creatinine. The kidney allograft biopsy was consistent with C3GN. He was started on Acthar® 80 units subcutaneous twice weekly and the proteinuria was reduced to >50% within 2 months of therapy. When ecucilizumab 900 mg IV once weekly for 4 weeks was added with Acthar®, the proteinuria fully resolved within 10 weeks of treatment. Since then, the patient has been maintained on Acthar® monotherapy of 40 units subcutaneous twice weekly and has stayed in complete remission of proteinuria for more than a year till his last follow-up.

**Discussion:** In conclusion, this is the first case report describing the role of repository corticotropin as an effective therapy in reducing proteinuria and maintaining patients with C3GN in complete remission.

**PO2217**

Rare Presentation of Disseminated NocardiA as Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in Renal Transplant

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**Introduction:** Nocardia is a rare opportunistic pathogen that typically affects the immunocompromised host. Recently, Williams et. al. reported a third of patients have disseminated cerebral nocardiosis at presentation with most common isolate Farcinica species. SIADH has been reported in association with disease progression.

**Case Description:** A 31-year-old renal transplant recipient presented 4 years post-transplant with dyspnea and left upper extremity jerking. Immunosuppressives (IS) included Mycophenolate, Tacrolimus and Prednisone. He had non focal exam. Blood work showed Na 129, Uosm 500 mosm/kg, UNa 92. MRI brain showed multiple lesions, largest in left frontal area. CT chest revealed right pleural effusion. Biopsy of resected brain abscess and pleural fluid analysis both confirmed Nocardia Araoensis and Bejingensis. Imipenem and Bactrim were started, IS regimen was tapered down. Repeat scans month later showed resolution of vasogenic edema, pleural effusion and SIADH.

**Discussion:** Cerebral nocardiosis is life-threatening opportunistic infection that often presents with no specific clinical signs to guide diagnosis. High index of clinical suspicion is the key to early diagnosis. Presence of SIADH should prompt search for Nocardia which needs to be identified down to its species for targeted antibiotic treatment.
Syndrome Post Transplant Nephrectomy Patient with Subsequent Immune Reconstitution Inflammatory Disseminated Mycobacterium Avium Complex in a Renal Transplant

**PO218**

Disseminated Mycobacterium Avium Complex in a Renal Transplant Patient with Subsequent Immune Reconstitution Inflammatory Syndrome Post Transplant Nephrectomy


**Introduction:** Mycobacterium avium Complex (MAC) are a group of pathogenic mycobacteria present in soil and water. Infection can present with respiratory symptoms, but in immunocompromised patients disseminated disease with fevers, weight-loss or diarrhoea is more common. Immune Reconstitution Inflammatory Syndrome (IRIS) is an excessive but protective inflammatory response against an existing pathogen when immune function is restored. It is usually seen in patients with Human Immunodeficiency Virus but has been described in renal transplant patients with MAC infection. It can lead to hypercalcaemia via increased macrophage 1α-hydroxylase activity, causing increased 1,25(OH)2D3 production.

**Case Description:** A 54-year-old male presented 3 years post renal transplant with recurrent fevers, night sweats and pancytopenia with a haemoglobin of 76 g/L, leucocytes of 1x109/L and platelets of 72x109/L. He was on Tacrolimus, Mycophenolate and Prednisolone, and was previously treated with anti-thymocyte globulin for cellular rejection. Bone marrow and blood cultures were positive for MAC at 8 weeks. He was started on clarithromycin, ethambutol and rifampicin, with reduction in leucocytes of 1x109/L and platelets of 72x109/L. He represented 7 months later with fevers and 22lb weight loss. Extensive bloodwork was negative. Computed tomography showed cervical lymphadenopathy and mesenteric stranding. Non-necrotising granulomas were demonstrated on fine needle aspirate of both a cervical lymph node and bone marrow, in keeping with disseminated MAC. Tranplant nephrectomy was performed to allow cessation of immunosuppression. Renal histology showed granulomatous interstitial nephritis. He had ongoing fevers and hypercalcaemia for 1 month post nephrectomy with albumin corrected calcium of 3.32 μmol/L. Septic screen was negative. He was treated with oral prednisolone for suspected IRIS with resolution of symptoms.

**Discussion:** Disseminated MAC is a rare but life-threatening infection in renal transplant recipients that can require nephrectomy for cessation of immunosuppression. Non-tuberculous mycobacteria can take 6 weeks to culture and require specific culture media. Differentiation of IRIS vs drug resistance as a cause of persistent fevers is important.

**PO2220**

Simultaneous Occurrence of Actinomyces Gastritis and Severe Rejection in a Kidney Pancreas Transplant Recipient

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**Introduction:** We are presenting a 33 year old lady with history of Kidney Pancreas transplant admitted for rejection treatment and found to have co infection, actinomyces and CMV in gastric mucosa. Patient was managed well with modified net immunosuppression and discharged safely on long term antibiotics.

**Case Description:** 33 year old woman with h/o stage V CKD from type I diabetes mellitus had Simultaneous kidney pancreas transplant in 2018 admitted directly from clinic for rejection treatment. admission vitals were temperature 97 F, blood pressures of 151/99, heart rate 83, respiratory rate 18, on room air. exam unremarkable. home Immunosuppression is cyclosporine, sirolimus and prednisone. baseline creatinine
is 1.1-1.3 mg/dl. Admission creatinine is 5.0, BUN 33, lipase 290, amylase 124, cyclosporine level is 52, sirolimus level <2, interleukin cyles 332, HbA1C is 5.3, c peptide is 3.13. renal biopsy showed acute cellular rejection, moderate microvascular inflammation, C4d positive, acute antibody mediated rejection. Class I and II DSA were positive. she got 3 doses of solumedrol, 3 doses of thymoglobulin, 2 sessions of plasmapheresis. She was found to have group B streptococcal bacteremia. Removed central line. CT scan of abdomen and pelvis was done for chronic abdominal pain showed diffuse gastritis or infiltrative disease such as gastric lymphoma. EGD showed gastric ulcer with Actinomyces colonization. Biopsy of gastric mucosa showed reactive gastroptysis, purulent exudate, ample Actinomyces colonies, No lymphoma or cancer. CMV viral inclusions also seen. Serum CMV PCR negative. Further rejection treatment was placed on hold. Scheduled 2 doses of IV IG outpatient and resume mycophenolate mofetil as an outpatient after finishing antibiotics. Discharged with cyclosporine, prednisone, long term IV ampicillin, valcyte and follow up EGD in 4 weeks. Outpatient renal transplant biopsy was scheduled after completion of antibiotics to assess rejection. creatinine was plateaued around 3.4, lipase and amylase were normalized.

Discussion: Actinomycosis is considered an endogenous, opportunistic infection of immunocompromised patients. Incidence is about one per 500 000 (0.0002%) in developed countries. Prevalence of actinomycosis was around 0.02% in transplant recipients. Infections alter the management and outcome of graft rejections.

PO2222
Recurrent Renal Allograft Torsion After Simultaneous Kidney and Pancreas Transplantation: Is Still Possible to Salvage the Graft?
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Introduction: Kidney Allograft Torsion (KAT) is defined as a rotation of the renal allograft around its vascular pedicle. It is a rare complication with high rate of graft loss. The non-specific presentation and inability to provide a definitive diagnosis by imaging, mainly in cases of partial torsion, often delay the diagnosis and treatment. We report a case of recurrent complete torsion of the renal allograft after simultaneous kidney and pancreas transplantation (SKPTx), requiring two emergency exploratory laparotomies.

Case Description: A 38-year-old woman with a history of intraperitoneal SKPTx underwent two separate emergency exploratory laparotomies secondary to complete renal allograft torsion, respectively seven and eleven months after the transplant. In both episodes, no adhesions were encountered. During the first operation, nephropexy was performed. During the second operation, an abdominal wall mesh was placed and fixed to the abdominal wall. Acute kidney injury (AKI) related to KAT recovered in both occasions with a creatinine of 1.3 mg/dl at four months follow-up.

Discussion: Renal torsion should be always suspected in intraoperatively placed kidneys presenting with nonspecific symptoms, abdominal pain, oliguria and worsening kidney function. Surgical exploration should be considered to salvage the renal graft. This case illustrates the reversibility of a severe injury related to this vascular complication with an adequate return to baseline kidney function even when diagnosis and surgical treatment of KAT might be delayed secondary to its misleading clinical presentation.

PO2223
Immunosuppression Cessation During Chemotherapy for Post-Transplant Lymphoproliferative Disorders in Kidney Transplant Recipients
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Introduction: Kidney transplant patients have a 20-fold higher risk to develop Post-Transplant Lymphoproliferative disorder (PTLD). PTLD requires reduction in immunosuppression (IS) medications to the lowest dose that prevents rejection. Here we report the safe withdrawal of IS in three kidney transplant recipients with PTLD receiving chemotherapy.

Case Description: Case 1: A 44-year-old male received a deceased donor renal transplant with alemtuzumab induction. He developed cellular rejection that was treated with steroids and thymoglobulin. He was maintained on cyclosporine, mycophenolate, and prednisone. Later on, he developed resistant EBV viremia and a retroperitoneal mass with diffuse lymphadenopathy. Biopsy revealed a high-grade, EBV-negative, monomorphic diffuse large B cell lymphoma (DLBCL). IS medications were stopped except for low-dose prednisone. Creatinine remained stable post six cycles of chemotherapy, with complete response after three cycles. Case 2: A 59-year-old male with a history of membranous nephropathy (MN) treated with rituximab. He received a living-related donor renal transplant and was treated with modified Ponticelli protocol. He was maintained on cyclosporine and mycophenolate. Ten years post-transplant, he had a large mesenteric soft tissue mass with lymphadenopathy. Biopsy showed EBV-negative, monomorphic high-grade DLBCL. IS medications were stopped. The patient received six cycles of chemotherapy and achieved a complete response. Creatinine remained at baseline. Case 3: A 36-year-old male with a history of IgA nephropathy, received a LDLRT with alemtuzumab induction. He was maintained on tacrolimus and mycophenolate. Five months later, he was diagnosed with stage IIIIB, EBV-positive, monomorphic DLBCL via tonsillar mass biopsy. IS medications were stopped and he went into complete remission after eight cycles of chemotherapy. He was started on sirolimus monotherapy post-chemotherapy. Creatinine remained at baseline for five years.

Discussion: IS withdrawal seems to be a safe option during chemotherapy for PTLD. Chemotherapy causes prolonged immunosuppression or immune tolerance to the allograft. The safe cessation of IS while receiving chemotherapy for PTLD has been described, with remission of low-dose IS post-remission.

PO2224
Sirolimus and Chylorperitoneum: A Rare Pair
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Introduction: The mammalian target of rapamycin inhibitors (mTOR) are associated with complications like hyperlipidemia, lymphocytopenia, lymphedema and rarely chylous ascites (CA), characterized by a milky colored, triglyceride (TG) rich fluid leading to dehydration, electrolytes imbalances and immunosuppression. We present a case of sirolimus induced chylorperitoneum in an ESKD patient.
Case Description: 44 year old woman with heart failure reduced ejection fraction (HFrEF) secondary to transposition of great vessels and orthotopic heart transplant in 2007, NASH cirrhosis and ESKD from calcineurin inhibitor toxicity, switched to sirolimus in 2018. Renal function declined requiring initiation of peritoneal dialysis (PD) in December 2020. 3 months prior patient presented with right upper extremity (RUE)/ipsilateral breast swelling, erythema and dull pain. US doppler ruled out DVT. Lymphangiography/cellulitis was suspected, started antibiotics with some improvement. Lymphoscintigram showed diffuse skin/right breast soft tissue edema. PD catheter was placed, incidentally found mild clear ascites, liver cirrhosis and bilateral ovarian cysts, work up for malignancy was negative and discharged. She trained for PD and efficient for KT/V had milky appearance. Fluid analysis showed nucleate cell count 1151mcL, RBCs 1391mcL, total protein 2.4g/dl, albumin 1g/dL, amylase <30u/L, glucose 160mg/dL, LDH 248IU and TG level 141mg/dl consistent with CA. Sirolimus was held and 2 weeks after PD fluid cleared and RUE lymphedema slowly improved with right breast enlargement to date.

Discussion: CA results from disruptive lymphatic system and posterior leakage of lymph into the abdominal cavity. Diagnosis requires TG levels >110mg/dl and gold standard imaging test is lymphangiography. Multiple etiologies are proposed: malignancy, traumatic surgical injury, liver cirrhosis and cardiovascular disease. Less common, mycobacterium infections and medications (mTORi, calcium channel blockers). Sirolimus causes disruption in proliferative signals required to seal perivascular lymphatics leading to high rates of lymphedema/lymphoceles. This explains RUE/ipsilateral breast swelling and disruption in proliferative signals required to seal perivascular lymphatics leading to high rates of lymphedema/lymphoceles. This explains RUE/ipsilateral breast swelling.

Renal Transplant Recipient with Large Periorbital Basal Cell Carcinoma (BCC) Cured Nonsurgically with Vismodegib

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Introduction: Renal transplant recipients (RTR) live a delicate balance between preserving allograft function with immunosuppression medications (IS) and the side effects (e.g malignancies), Skin cancers are prevalent with Squamous (SCC) & BCC (SCC), comprising 90% of skin cancers. These tumors are aggressive, exhibiting unique pathophysiologic characteristics. We present a case of a RTR who developed invasive peribitol BCC; successfully treated with novel chemotherapeutic Vismodegib.

Case Description: A 66-year-old man with history of kidney transplant had a stable graft function with Cr 1.6 on IS for 35 years, on Prednisone and Tacrolimus. with a history of recurrent SCC and BCC treated with surgical and radiation therapy. During clinic, he was found to have a large tumor in the lateral canthus of the left eye. Patient was referred to dermatology, biopsy revealed BCC. The unpredictable nature of tacrolimus pharmacokinetics has led to the development of extended-release tacrolimus such as Envarsus XR (8, 9, 12). While data is lacking, Envarsus XR is thought to have a lower incidence of neurotoxic side-effects (10, 11). To our knowledge, there are no recorded cases in the literature of psychosis related to Envarsus XR.

Discussion: This case presents a unique instance of extended-release tacrolimus induced psychosis. While immediate-release tacrolimus is well known to cause neurotoxicity (5, 13), extended release is generally felt to be safer (12, 9). This case illustrates that while extended-release Tacrolimus formulations may have a reduced incidence of neurological side effects, they are not devoid of them. The SIMPLE trial is currently ongoing and its data may shed more light on tacrolimus induced neurotoxicity (10). Regardless of the outcome of this research, the treatment for tacrolimus induced neurotoxicity should always be to decrease the dose or withdraw the medication (14).

PO2226

Psychosis as a Neurotoxic Manifestation of Extended-Release Tacrolimus

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Introduction: Tacrolimus is a calcineurin inhibitor used in renal transplant to reduce the risk of rejection. Common side effects include infection, nephrotoxicity, and neurotoxicity (7). The neurotoxic effects can manifest as psychosis, paranoia, and bipolar mania (4, 2). The unpredictable nature of tacrolimus pharmacokinetics has led to the development of extended-release tacrolimus such as Envarsus XR (8, 9, 12). While data is lacking, Envarsus XR is thought to have a lower incidence of neurotoxic side-effects (10, 11). To our knowledge, there are no recorded cases in the literature of psychosis related to Envarsus XR (3,6).

Case Description: Ms. H is a 62 year old woman who underwent allogenic renal transplant and was placed on immediate-release tacrolimus 0.5 mg twice daily. Due to high tacrolimus levels (average 9.6 ng/ml) she was switched to Envarsus XR 0.75 mg daily and subsequently reported new onset emotional disturbance. She was initially treated with fluoxetine then switched to citalopram without relief. She then developed paranoid ideation and refused to sleep. The patient and family felt this behavior correlated with starting Envarsus XR. This was discussed with her transplant team and Envarsus XR was continued as her tacrolimus levels were within goal (average 5.3 ng/ml). Her paranoia worsened and she was seen by psychiatry and placed on risperidone 2 mg daily. She continued to experience paranoid delusions and behavioral disturbance. She was then switched from Envarsus XR back to immediate-release tacrolimus and had complete resolution of symptoms. Her current average tacrolimus level is 5.05 ng/ml.

Discussion: This case presents a unique instance of extended-release tacrolimus induced psychosis. While immediate-release tacrolimus is well known to cause neurotoxicity (5, 13), extended release is generally felt to be safer (12, 9). This case illustrates that while extended-release Tacrolimus formulations may have a reduced incidence of neurological side effects, they are not devoid of them. The SIMPLE trial is currently ongoing and its data may shed more light on tacrolimus induced neurotoxicity (10). Regardless of the outcome of this research, the treatment for tacrolimus induced neurotoxicity should always be to decrease the dose or withdraw the medication (14).

PO2227

Deep Learning Identifies Pathological Abnormalities Predictive of Graft Loss in Kidney Transplant Biopsies

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Background: Interstitial fibrosis, tubular atrophy, and inflammation are major contributors to renal allograft failure. Here we seek an objective, quantitative pathological assessment of these lesions to improve predictive utility.

Methods: We constructed a deep-learning-based pipeline recognizing normal vs. abnormal kidney tissue compartments and mononuclear leukocyte (MNL) infiltrates from whole-slide images. We calculated the proportion of renal tissue comprised by interstitium (ITAS), tubules (TAS), and MNLs. Our model accurately recognized kidney tissue compartments and MNLs from whole-slide images, achieving >90% accuracy. We used deep learning to detect and quantify pathological interstitial fibrosis, tubular atrophy, and MNL infiltration, achieving >90% accuracy. We then performed a retrospective study of 336 kidney transplant biopsies from 2014 to 2018, evaluating the proportion of renal tissue comprised by interstitium (ITAS), tubules (TAS), and MNLs. Our model accurately recognized kidney tissue compartments and MNLs from whole-slide images, achieving >90% accuracy. We then performed a retrospective study of 336 kidney transplant biopsies from 2014 to 2018, evaluating the proportion of renal tissue comprised by interstitium (ITAS), tubules (TAS), and MNLs.

Results: Our model correctly identified normal kidney tissue compartments and MNLs. The deep features significantly correlated with Banff scores, but were more sensitive to subtle pathological changes below the thresholds in Banff scores. The Interstitial and Tubular Abnormality Score (ITAS) in baseline samples was highly predictive of 1-year graft loss (p=2.3e-05), while the Composite Damage Score (CDS) in 12-month post-transplant biopsies predicted lower graft loss (p=7.3e-05). CDS outperformed Banff score or clinical predictors with superior graft loss prediction accuracy. High intermediate risk groups stratified by ITAS or CDS also demonstrated significantly higher incidence of eGFR decline and subsequent graft failure.

Conclusions: This deep-learning approach accurately detected and quantified pathological lesions from baseline or post-transplant biopsies, and demonstrated superior ability for prediction of post-transplant graft loss with potential application as a prevention, risk stratification or monitoring tool.

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PO2228
Dual Diagnosis of Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome in Pregnancy
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Introduction: Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uraemic syndrome (aHUS) are thrombotic microangiopathy (TMA) disorders which may initially occur in pregnancy. TTP, caused by severe ADAMTS13 deficiency, is treated with plasma exchange (TTP); whereas aHUS, caused by uncontrolled complement activation, is treated with complement inhibition (e.g., eculizumab). Because TTP and aHUS have different causes, the term TTP-HUS is no longer used. However, we describe a patient diagnosed and treated for both TTP and aHUS in pregnancy.
Case Description: A 36-year-old female at 9 weeks’ gestation presented with hematuria. Labs revealed severe thrombocytopenia (platelets 5 k/ul), hemolytic anemia, and acute kidney injury. TTP was suspected, so PEX was initiated, but she did not fully respond (Fig 1). ADAMTS13 activity was low (11%) but with negative inhibitor, arginine variants were identified as genetic testing revealed no mutations. Complement mediated TMA (aHUS) was considered given low C3, C4, and proteinuria; Lupus and Anti-Phospholipid Syndrome were ruled out. Genetic testing revealed a rare C3 variant and polymorphisms in CFH and MCP, which are enriched in aHUS patients. After multidisciplinary review, the diagnosis of aHUS was made. PEX was stopped, and eculizumab was started with good response. At 35 weeks’ gestation she presented with hypertension and petechiae, and labs showed recurrence of hemolytic anemia and thrombocytopenia (platelets 7 k/ul). She had cesarean delivery, after which PEX was initiated given renewed concern for TTP. ADAMTS13 activity was <5% with positive inhibitory antibody, now confirming acquired TTP. Eculizumab was stopped, and she received 14 cycles of PEX, prednisone, and rituximab for refractory TTP (Fig 1). Treatments were stopped after 6 weeks, and she remains in remission after 1 year.
Discussion: This case illustrates dual diagnosis of TTP and aHUS in pregnancy. Key points: a) Rarely, TTP and aHUS may coexist; b) ADAMTS13 activity and complement genetic testing may help identify TMA etiology; and c) Treatment of TMA in pregnancy with PEX or complement inhibition should be clinically-based.

PO2229
Pregnancy-Associated Atypical Hemolytic Uremic Syndrome in the Setting of a Rare THBD Mutation and Successful Treatment with Eculizumab
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Introduction: Pregnancy-associated atypical hemolytic uraemic syndrome (PaHUS) is a rare but fatal thrombotic microangiopathy that results from uncontrolled complement activation during the peripartum and postpartum periods. Underlying complement gene mutations are found in a majority of cases. THBD, the gene responsible for encoding thrombomodulin, is a known risk variant associated with PaHUS. We present a case of PaHUS complicated by intratendine fetal demise and acute renal failure in the setting of a rare THBD gene variance which was successfully treated with the terminal complement inhibitor eculizumab.
Case Description: 20-year G1P0 female presented at 30w4d with severe abdominal pain and diffuse vaginal bleeding. An emergent cesarian section revealed a placental abruption with intratendine fetal demise. Hospital course was complicated by anuria with a maximum serum creatinine 8.43 mg/dl, hemoglobin 5.5 g/dl, platelets 15 x10^3/ul, lactate dehydrogenase 9051 U/L, and schistocytes seen on peripheral smear. She was initiated on renal replacement therapy, daily plasma exchange, and steroids. Despite this, she experienced persistent hemolysis, dialysis dependence, and worsening respiratory failure ultimately requiring intubation. ADAMTS13 activity was normal at 83%. Eculizumab was initiated, and after one week, hematologic parameters normalized with evidence of renal recovery. Outpatient genetic testing revealed a rare variant in THBD. Six months following discharge, the patient remains in remission on maintenance eculizumab.
Discussion: The diagnosis of PaHUS is very challenging; however, prompt recognition and subsequent genetic testing for complement variants are crucial given association with more severe outcomes, progression to ESRD, and increased risk of relapse. Pathologic variances in THBD account for 5% of aHUS cases and have been associated with earlier onset and higher mortality; however, risk of disease relapse with mutations in this gene is unknown. Although eculizumab has been shown effective in PaHUS, there is little data on treatment duration and recurrence rate with therapy in subsequent pregnancies. Further expansion of genetic testing is required to enhance our knowledge of all PaHUS susceptibility factors and improve management of patients similar to the presented case.

PO2230
Efficacy of Eculizumab Therapy in Delayed-Diagnosed, Hemodialysis-Dependent, Pregnancy-Triggered, Complement-Mediated Thrombotic Microangiopathy
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Introduction: Pregnancy associated atypical hemolytic uraemic syndrome (p-aHUS) is prevalent in pregnancy and affects 1/25,000 pregnancies in the general population. The delivery is vital for halting the disease process. The course of complement-mediated thrombotic microangiopathy(C-TMA) is not affected by delivery, but condition improves with anti-complement therapy. We are presenting a rare case of delayed diagnosed, pregnancy provoked C-TMA with significant improvement in blood pressure, stabilization of anemia, and resolution of thrombocytopenia after treatment with Eculizumab.
Case Description: A 25-year-old Hispanic woman with history of CKD stage IIIIB presented with syncope. She developed renal failure, required hemodialysis (HD) and HTN during her first pregnancy. During postpartum, HD was stopped and HTN resolved. Two years later she was admitted with worsened renal function, severe anemia (Hb 4 g/dl), thrombocytopenia (36k/ul), and poor controlled HTN, needing 6 different classes of drugs to control her blood pressure. Blood smear showed schistocytes. Our extensive work up ruled out: TTP, HUS, DIC, lupus, scleroderma, and other disorders. Complement was low. Lupus anticoagulant was positive, anti-cardiolipin, and anti-beta-2-glycoprotein-1. The simultaneous presence of all three antibodies is associated with the highest risk of thrombotic complications in APS.
Discussion: Timely diagnosis and management are the key points to improve C-TMA prognosis. It may be a difficult diagnosis and mimic eclampsia, HELLP syndrome, or p-aHUS. Although it is related to inherited defects of complement alternative pathway or the proteins that regulate it, lack of linked gene mutations cannot exclude C-TMA. In this patient, the diagnosis of C-TMA was not made until two years after onset. Our case report showed that even though Eculizumab cannot completely reverse the renal injury at the late stage of C-TMA, it may still improve the blood pressure control, normalize platelets, help anemia, and prevent further complications.

PO2231
Therapeutic Plasma Exchange Improved Pregnancy Outcomes in a Patient with Triple Positive Anti-Phospholipid Antibody Syndrome
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Introduction: Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by antibodies directed against platelet, monocyte, endothelial cell, and trophoblast moieties potentially causing venous and arterial thromboses. The placental vasculature is particularly vulnerable to these antibodies resulting in a marked increased risk of fetal growth restriction, placental infarction, abortion, stillbirth, and preterm severe preeclampsia. APS is diagnosed by clinical criteria in conjunction with laboratory findings, and the circulating anti-phospholipid antibodies commonly tested are lupus anticoagulant, anti-cardiolipin, and anti-beta-2-glycoprotein-1. The simultaneous presence of all three antibodies is associated with the highest risk of thrombotic complications in APS.
Case Description: A 29-year-old nulligravid with medical history was significant for APS on lifelong coumadin. Her APS labs at the time of conception visit showed elevated lupus anticoagulant ratio, anticardiolipin and anti-beta-2-glycoprotein-lantibodies (Triple- positive antibodies). Medications included twice daily LMWH 60 mg and hydroxychloroquine 200 mg. Fetal anatomic survey at 20 weeks demonstrated normal fetal growth, however, by 21 weeks 6 days ultrasound showed absent-end diastolic flow of the umbilical artery Doppler waveform. She was admitted to the hospital. A pre-eclampsia workup was completed due to hypertension and new onset proteinuria. LDA daily, pravastatin 20mg was added. Due to the diagnosis of preeclampsia with severe features, the decision was made to treat with therapeutic plasma exchange.
Discussion: High-risk obstetric APS profiles are linked to specific serological markers such as triple antibody positivity, clinical features such as a history of thrombosis, and the presence of pregnancies result in a liveborn infant, with that rate dropping to 30% in patients who are triple systemic autoimmune diseases. Therapeutic plasma exchange every 48 hours successfully prolonged the pregnancy for 11 weeks, resulting in an optimal pregnancy outcome for both mother and infant given the initial dire clinical situation at a pre-viable gestation. The rationale for TPE every 48 hours was based on the experience in plasmapheresis use in Catastrophic Antiphospholipid Syndrome (CAPS)
PO2232
Lupus Nephritis Kidney Biopsy Characteristics and Preterm Birth
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Background: Lupus nephritis (LN) in pregnancy is associated with high rates of preterm birth (PTB). Hypocomplementemia, elevated creatinine, proteinuria and hypertension serve as risk factors. Outside of pregnancy, class IV LN and interstitial fibrosis at initial biopsy associate with progressive disease. We performed a retrospective chart review to assess if timing of kidney biopsy and histologic features increased PTB.

Methods: We included women with LN enrolled in the Glomerular Disease Collaborative Network registry who delivered at University of North Carolina (UNC) Hospital from 2001-2019. Delivery data came from the UNC perinatal database. Fishers exact test assessed biopsy characteristics and PTB (< 37 weeks).

Results: There were 36 deliveries in 32 women. Figure 1 describes the cohort. Among preconception biopsies (n=25), pregnancy occurring ≤ 24m after biopsy was more likely to result in PTB than if biopsy was performed > 24m prior to conception (82% vs 29%, p < 0.02). A UPUR > 0.5 mg/g in the first trimester was also associated with PTB (81% vs 36%, p = 0.04). PTB occurred in 69% with proliferative LN vs 50% without (ie primary class diagnosis II or V), p=0.84. Class IV LN was not significantly associated with PTB; neither was the presence of crescents (n=21/36), activity ≥ 6 (n=16-27), or more than mild interstitial sclerosis (n=6/33).

Conclusions: Biopsy occurring within 2 years of conception and first trimester proteinuria were significantly associated with PTB. While this presumes greater LN activity, no specific biopsy characteristic impacted the outcome. This data may aid in preconception counseling for optimal timing of conception. Calciuminibitors were not used in the first trimester in this cohort; their antiproteinuric qualities and effect on PTB requires evaluation.

PO2233
Second Trimester eGFR and Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus
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Background: Adverse pregnancy outcomes are more common in women with SLE. 2nd trimester eGFR was shown to predict adverse pregnancy outcomes in a general population cohort. We sought to evaluate 2nd trimester eGFR as a predictor of adverse pregnancy outcomes in women with SLE.

Methods: We evaluated 684 women with SLE(22% of Black race) who received care in North America and Europe from 1995-2017. 2nd trimester eGFR was stratified based on studies demonstrating women with an eGFR 120-135 ml/min/1.73m2 had the lowest odds of adverse outcomes. Outcomes of interest included preterm birth, preeclampsia, fetal loss and poor pregnancy outcome(composite outcome). 2nd trimester GFR was computed using the CKD Epi equation without adjustment for race. In sensitivity analysis, 2nd trimester GFR computed using the conventional race-based equation. Polynomial and logistic regression models used to evaluate 2nd trimester eGFR and adverse outcomes.

Results: Very low eGFR(<90ml/min/1.73m2)and very high eGFR (>135ml/ min/1.73m2)were associated with higher adverse outcomes. In univariate and multivariable regression models adjusted for age, race, and SLE disease activity, very low eGFR was associated with preterm birth, preeclampsia, fetal loss and poor pregnancy outcome. Very high eGFR was associated with poor pregnancy outcome and preterm birth. In sensitivity analyses using race based GFR estimates, very low eGFR remained associated with adverse outcomes observed. No association was observed between very high eGFR and adverse outcomes.

Conclusions: We found a U-shaped relationship between 2nd trimester eGFR and adverse pregnancy outcomes. Women with eGFR <90ml/min/1.73m2 and >135ml/min/1.73m2 had higher odds of adverse outcomes. 2nd trimester eGFR may be a helpful tool to identify women with SLE at greater risk for adverse outcome. Our results further suggest that kidney hyperfiltration may become pathologic during pregnancy. There were notable differences using non-race based and race-based GFR estimating equations. These differences may have clinical implications when utilizing GFR estimating equations to predict health outcomes.

Funding: Private Foundation Support

Association of 2nd Trimester eGFR and Adverse Outcomes

PO2234
Comparison of Clinical Features of Pregnant and Non-Pregnant Women with Primary Hyperoxaluria
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Background: Primary hyperoxaluria (PH) is a rare monogenic disease characterized by oxalate overproduction in the liver, hyperoxaluria, and risk of kidney stones and chronic kidney disease. Data about the effects of pregnancy on women with PH are lacking. We aimed to compare clinical features and risk of incident kidney failure in women with PH with and without pregnancy.

Methods: Women with PH were identified from the Rare Kidney Stone Consortium registry, and pregnancy was identified by phone interview and medical record review. Kidney survival and risk of time-dependent kidney failure were estimated using the Kaplan-Meier method and adjusted proportional hazard Cox’s model.

Results: We identified 47 women with PH with a history of pregnancy and 39 women without pregnancy. PH was diagnosed later in women with pregnancy vs. women without pregnancy (median age 32.4 vs. 13.4 years, p<0.001). Other clinical characteristics such as PH type, eGFR and 24-hour urine oxalate excretion (Uox) at PH diagnosis did not differ between the 2 groups. Fig 1A shows the time course of the PH diagnosis, pregnancy and kidney failure in 29 women with known delivery date. In women with pregnancy versus non-pregnancy, the hazard ratio for incident kidney failure was 0.81 (95% CI 0.25-2.6, p=0.73) when adjusted for PH type, age, and eGFR and Uox at PH diagnosis. Among patients with PH1 who did not have kidney failure by the time of the 1st pregnancy (n=20), kidney survival estimates at 10, 20, and 30 years after delivery were 79%, 60%, and 45%, respectively (Fig 1B).

Conclusions: These results suggest that pregnancy did not greatly impact renal prognosis in women with PH.

Funding: Other NIH Support - NIH grant U54KD083908, Commercial Support - The Oxalosis and Hyperoxaluria Foundation, a non-profit patient advocacy group

Methods: Women with PH with and without pregnancy (median age 32.4 vs. 13.4 years, p<0.001). Other clinical characteristics such as PH type, eGFR and 24-hour urine oxalate excretion (Uox) at PH diagnosis did not differ between the 2 groups. Fig 1A shows the time course of the PH diagnosis, pregnancy and kidney failure in 29 women with known delivery date. In women with pregnancy versus non-pregnancy, the hazard ratio for incident kidney failure was 0.81 (95% CI 0.25-2.6, p=0.73) when adjusted for PH type, age, and eGFR and Uox at PH diagnosis. Among patients with PH1 who did not have kidney failure by the time of the 1st pregnancy (n=20), kidney survival estimates at 10, 20, and 30 years after delivery were 79%, 60%, and 45%, respectively (Fig 1B).

Conclusions: These results suggest that pregnancy did not greatly impact renal prognosis in women with PH.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

683
Narrowing Communication Gaps to Optimize Patient-Centered Pregnancy Counseling for Women with CKD
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Background: Women with chronic kidney disease (CKD) face unique pregnancy decision-making challenges. Although there is an increased risk of adverse pregnancy outcomes in women with CKD, many women report strong pregnancy desires. There is little evidence on how to support pregnancy communication and decision-making needs in women with CKD.

Methods: We performed semi-structured interviews with 18-45 years of age who have CKD stages I-V (n=30), and their practicing nephrologists (n=12) at one academic medical center. The average age of patients was mean(SD) 32.4(6.9) years; 50% already had children. 50% (n=15) identified as White, 26.7% (n=8) as Black, 13.3% (n=4) as Hispanic, 6.7% (n=2) as Asian, and one declined to answer. CKD etiologies included lupus nephritis (n=7, 23.3%), other nephrotic/nephritic syndromes (n=9, 30%), diabetes (n=4, 13%), hypertension (n=3, 10%), other (n=4, 13%), and unknown (n=3, 10%). Interview questions probed patients about counseling experiences and reproductive health in CKD, approaches to pregnancy decision-making, barriers and facilitators to effective counseling, and desires for future support. A codebook was iteratively developed, with double coding of transcripts and discrepancies resolved via consensus.

Results: Most women with CKD preferred their nephrologist introduce the concept of reproductive planning to elicit their values in care and reduce barriers to pregnancy counseling. Specific information about individual pregnancy risks and risks to potential offspring were desired. Women with strong reproductive intentions more often sought pregnancy information and indicated a higher risk tolerance especially when compared to physicians. Among women considering pregnancy, discussion of risks alone without discussion of strategies to manage or mitigate risks was perceived as alienating. Nephrologists acknowledged importance of patient pregnancy desires, however, prioritized decision-making communication about absolute numerical risks to patients, and expressed high risk-aversion.

Conclusions: Patient-provider pregnancy communication and decision-making are critical for women who have CKD. Further research is needed to ensure nephrologists have tools to support pregnancy decision-making that incorporates patients’ needs, values and goals in care.

Funding: NIDDK Support

Maternal Hypertension and Hypertensive Disorders of Pregnancy Are Associated with Increased Risk of Hypertension in Offspring

Background: Hypertensive disorders of pregnancy (HDP) have significant effects on perinatal outcomes for offspring. Although there is increasing evidence of adverse effects of HDP exposure on long-term health outcomes in offspring, the impact of maternal hypertension beyond HDP is limited.

Methods: We performed a population-based cohort study of 7544 women with 8755 pregnancies from 1976 to 1982. HDP during each offspring’s birth was identified as, Level 1: pathogenic; Level 2: likely pathogenic; Level 3: variant of uncertain significance (VUS); Level 4: likely benign; Level 5: benign.

Variants were classified on the basis of clinical significance, according to published American College of Medical Genetics guidelines. Based on these standards, variants are classified as, Level 1: pathogenic; Level 2: likely pathogenic; Level 3: variant of uncertain significance (VUS); Level 4: likely benign; Level 5: benign.

Results: At the time of index pregnancy with HDP syndrome, patients were 36 ± 5 years old; twelve of 15 (80%) were nulliparous, and delivery occurred at 34 ± 5 weeks gestation. Five of 15 patients (33%) had a pathogenic variant, 9 (60%) had a variant of uncertain significance (VUS), and one (7%) had a variant benign. Homozygous deletion of CFHR1-CFHR3 was detected in four patients. Fifteen unique missense variants were detected in various genes, including C3, CFD, CFH, CFHR2, CFHR5, CFI, MASF2, and PLG. One patient with a pathogenic variant developed recurrent severe preeclampsia and one patient with a VUS developed recurrent HELLP syndrome.

Conclusions: These results reveal that overactivity of the complement system, due to an underlying genetic variant, may define a subset of patients that develop preeclampsia and HELLP syndrome. Long-term follow-up of these patients is needed to evaluate the risk for future cardiovascular and kidney disease.
Results: 44 pregnancies and 34 deliveries were identified. Non-live birth pregnancy outcomes included eight miscarriages, one ectopic pregnancy and one elective abortion. The presumed driver of disease was known for eight patients; gene variants of unknown significance (n=3), nephritic factors (n=4), and a monoclonal protein (n=1). Six patients presented first C3G symptoms during pregnancy. Preeclampsia developed in 11. Six infants were premature. Five were born with low birthweight. One infant suffered a stroke. One infant presented with AKI. [Maternal nephritic factor was identified in neonatal sera.]

Conclusions: We provide a summary of maternal-fetal outcomes in C3G mothers. Our data supports an increased risk of preeclampsia in C3G mothers as compared to healthy controls. There was no excess risk of miscarriage, cesarean section, ectopic pregnancy, prematurity, or low birth weight. This data indicates a relatively higher risk of preeclampsia and lower risk of cesarean section compared to women with IgA Nephropathy. A similar risk of miscarriage, prematurity, and low birth weight as other glomerular diseases was evident. Our data supports a reasonable maternal-fetal risk profile for C3G patients.

Figure 1- Peri-Pregnancy Outcomes in C3G Mothers

Table 1: Peri-Pregnancy Outcomes in C3G Mothers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C3G (n=34)</th>
<th>Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>11/34 (32%)</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>11/34 (32%)</td>
<td>5/50 (10%)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>9/34 (26%)</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>11/34 (32%)</td>
<td>5/50 (10%)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>11/34 (32%)</td>
<td>5/50 (10%)</td>
</tr>
<tr>
<td>NICU stay</td>
<td>10/34 (29%)</td>
<td>2/50 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24/34 (70%)</td>
<td>20/50 (40%)</td>
</tr>
<tr>
<td>Hemorrhagic complications</td>
<td>2/34 (6%)</td>
<td>1/50 (2%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>17/34 (50%)</td>
<td>13/50 (26%)</td>
</tr>
</tbody>
</table>

PO2239
Maternal Health in Autosomal Dominant Tubulointerstitial Kidney Disease
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Background: Autosomal dominant tubulointerstitial kidney disease due to MUC1 mutations (ADTKD-MUC1) and UMOD mutations (ADTKD-UMOD) are becoming increasingly recognized as causes of chronic kidney disease (CKD). Genetic testing allows women to determine if they are affected with these conditions, and data on the outcomes in pregnancy in ADTKD would be of great interest to them as they prepare for future pregnancies.

Methods: We surveyed women with ADTKD and genetically unaffected family disease as regards past pregnancy outcomes. We also analyzed survival to end-stage kidney disease (ESKD) according to number of pregnancies.

Results: We received completed standardized questionnaires surveys from 52 women with ADTKD-MUC1 (113 pregnancies), 74 women with ADTKD-UMOD (136 pregnancies), and 35 genetically unaffected women (64 pregnancies). At the time of pregnancy, only 16.5% of genetically affected women were aware that they had ADTKD. Results are summarized in Table 1. There was a nonstatistical increase in HTN and hospitalization for HTN. 10% of births to affected mothers were premature vs. 0% in unaffected mothers, but child outcomes were good. Survival analysis showed no statistical differences in age to ESRD based on number of pregnancies for affected women. There was a nonstatistically significant difference in the prevalence of AKI in transmasculine individuals who received GAHT as compared to transmasculine individuals who did not receive exogenous GAHT; no such difference was found with CKD. In the transmasculine population, there was no statistically significant association of exposure to GAHT with prevalence of AKI or CKD. Future studies should determine whether the prevalence of AKI in transmasculine individuals who received GAHT as compared to transmasculine individuals who did not receive exogenous GAHT is associated with kidney injury.

Conclusions: Past pregnancy is associated with larger kidneys among healthy women suggesting that the enlargement of kidneys with pregnancy does not fully resolve after delivery. Among healthy post-menopausal women, longer duration of menopause and shorter reproductive lifespan associated with detectable IFTA on kidney biopsy consistent with a protective effect of estrogen on preventing subclinical kidney injury.

Funding: NIDDK Support, Clinical Revenue Support

PO2240
Effect of Reproductive History on Kidney Structure and Function in Women
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Background: Varying estrogen levels from menarche to menopause and physiological changes of pregnancy may impact kidney health in women.

Methods: Female kidney donors from 2000 to 2017 were sent a survey on reproductive history, including menarche, pregnancy, and menopause. At the time of donation, donors had a medical evaluation, measured GFR, 24h urine albumin, CT angiography of kidneys, and a kidney biopsy. Kidney volumes were calculated from CT images. Non-sclerosed and globally sclerosed glomeruli counts and % interstitial fibrosis/tubular atrophy (IFTA) were assessed via kidney biopsy. Kidney function and structural findings at the time of donation were assessed by differences in reproductive factors prior to donation adjusting for age.

Results: There were 673 women studied with a mean (SD) age at donation of 47.4 (11.4) and 74% had at least one pre-donation birth. As compared to non-parous women, parous women had a higher total cortical volume (6.1%, p<0.009) and medullary volume (6.7%, p=0.038). However, among parous women, additional parity was not associated with further increases in kidney volumes. Among the 218 post-menopausal women, each year since menopause was associated with a higher likelihood of IFTA > 0% on biopsy independent of age (OR=1.052, p=0.027). With each 5-year increase in reproductive lifespan (years from menarche to menopause), there was a lower likelihood of having IFTA > 0% (OR=0.81, p=0.048). We did not find any significant association between past reproductive factors on GFR, urine albumin, glomerulosclerosis, or nephron number at the time of donation.

Conclusions: Past pregnancy is associated with larger kidneys among healthy women suggesting that the enlargement of kidneys with pregnancy does not fully resolve after delivery. Among healthy post-menopausal women, longer duration of menopause and shorter reproductive lifespan associated with detectable IFTA on kidney biopsy consistent with a protective effect of estrogen on preventing subclinical kidney injury.

Funding: NIDDK Support, Clinical Revenue Support

PO2241
Kidney Disease Prevalence in Transgender Individuals
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Background: Kidney disease in the transgender population is understudied which precludes the ability to derive appropriate care guidelines for promoting kidney health. The term transgender includes individuals for whom their assigned sex at birth doesn’t align with their gender identity. Transgender individuals often choose gender-affirming hormone therapy (GAHT) to achieve greater alignment. The impact of this necessary treatment on their kidney health has not been studied.

Methods: We performed a cross-sectional study of 360 transgender individuals, using medical records from 2009-2019. Diagnosis codes were used to identify individuals with acute kidney injury (AKI) and chronic kidney disease (CKD), and comparisons were performed between the groups.

Results: The mean age of the population was 42 (SEM 0.91) and 40% were of black race. Black individuals made up a greater proportion of the transmasculine population who received GAHT but a lower proportion of transmasculine individuals who received GAHT. The transmasculine population receiving GAHT had a higher proportion of non-white/non-black populations than in the overall transmasculine population. There was a statistically significant difference in the prevalence of AKI in transmasculine individuals who received GAHT as compared to transmasculine individuals who did not receive exogenous GAHT; no such difference was found with CKD. Transmasculine individuals who received GAHT showed a statistically lower prevalence of CKD than transmasculine individuals.

Conclusions: This single-center study of prevalence of kidney disease in the transgender patients demonstrates significant differences in kidney disease conditions in those who did vs. did not use GAHT. These studies highlight the need for further research to define the health and disease manifestations seen in the transgender population.

Funding: NIDDK Support
PO2242
Dietary Inflammatory Potential and the Risk of Incident ESKD in the Women’s Health Initiative
Tanya S. Johns,1,2 Yasmin Mossavar-Rahmani,1 James R. Hebert,3 Nora Frascchini,1 Michal L. Melamed,1,2 1Albert Einstein College of Medicine, Bronx, NY; 2Montefiore Medical Center, Bronx, NY; 3University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; 4University of South Carolina, Columbia, SC.

Background: Inflammation is implicated in the pathogenesis and progression of chronic kidney disease (CKD). Diet is an important modulator of chronic inflammation, and possibly kidney health. We evaluated the association of diet-associated inflammation with risk of incident end-stage kidney disease (ESKD) in the Women’s Health Initiative (WHI) study.

Methods: Participants enrolled between 1993-1998 in the Observational Study and Dietary Modification Trial of the WHI with completed food frequency questionnaires (FFQs), Medicare enrollment data, and serum creatinine (sCr) measurements were included in our study. Dietary inflammatory potential was assessed from FFQs using the dietary inflammatory index (DII®). The index has been previously validated in the WHI. Medicare claims data were used to ascertain ESKD status. Analyses used DII® scores adjusted for energy-intake (E-DII®), which were categorized into quartiles (Q): scores in Q1 (reference group) having the lowest dietary inflammatory potential and Q4 being the most pro-inflammatory. We performed multivariable Cox proportional hazards models adjusted for important covariates of interest to compare dietary quartiles for risk of incident ESKD. Participants were censored at the time of study withdrawal, loss-to-follow-up, or death.

Results: Of the 15,722 women included in our study, the mean age was 64.2 years (standard deviation 7.01); 35% self-identified as African American, 12% as Hispanic/Latinx, and 50% as White; 40% had hypertension and 9% had diabetes mellitus at baseline. The mean baseline sCr and estimated glomerular filtration rate were 0.74 mg/dL, and 89 ml/min/1.73m2, respectively. African American and Hispanic women compared to White women (30% vs 19%) were more likely to report consuming diets with scores in Q4. Over mean follow-up of 11.5 years, 515 women developed ESKD. Women with dietary patterns in Q4 compared to those in Q1 had a 20% higher risk of developing ESKD (hazard ratio 1.20 [95% confidence interval 1.05 – 1.38]; P=0.02) after adjusting for age, race/ethnicity, comorbidities, body mass index, education, medications, trials vs cohort study status, and region.

Conclusions: A pro-inflammatory dietary pattern is associated with a higher risk of new-onset ESKD among Medicare-eligible post-menopausal women without baseline CKD.

PO2243
Age-Stratified Sex Differences in the Risk of Cardiovascular Disease in Patients with CKD
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Background: In the general population, females (vs. males) and younger individuals have a lower cardiovascular risk. However, little is known whether this age- and sex-specific risk pattern of cardiovascular disease (CVD) translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if sex-specific risk of CVD differed across the age groups approximating premenopause (<45 y), perimenopause (45-54 y), and postmenopause (≥55 y) in patients with non-dialysis CKD who participated in the Chronic Renal Insufficiency Cohort (CRIC) observational study.

Methods: Cox proportional-hazards models were used to examine the age-stratified (<45 y, 45-54 y, and ≥55 y) association between sex and time to a composite of CVD events (heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease). Secondary outcomes were individual components of the CVD composite.

Results: The median follow-up time was 7 years. In the entire cohort, males had a 32% higher risk of incident CVD (95% CI: 1.15-5.3), Figure) than females after adjusting for age, race, clinic site, and traditional CVD risk factors, but not after further adjustment for markers of kidney disease (fully adjusted model). In the 45-54 y group, there was a 63% higher risk for CVD (95% CI: 4.1-15.7%) in males than females in the fully adjusted model. However, no sex-specific CVD risk was observed in the <45 y and ≥55 y groups in the fully adjusted model.

Conclusions: Our findings suggest that CKD may be a strong risk factor for CVD in females. Moreover, females may have a lower risk of CVD than males, particularly in the perimenopausal, but not premenopausal and postmenopausal ages.

Funding: NIDDK Support

PO2244
Elevated Triglyceride-Glucose Index Predicts Renal Hyperfiltration in Young Adults
Dongwhan Oh,1,2 Kang Yoon Lee,1,2 Eunji Yang,1,2 Hyeyong Cheon Park,1,2 Hoon Young Choi,1,2 Jong Hyun Jhee,1,2 Gangnam Severance Hospital, Seoul, Republic of Korea; 1Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.

Background: Insulin resistance increases the risk for renal hyperfiltration (RHF), a proposed mechanism for kidney injury in diabetes. However, the association between triglyceride-glucose (TyG) index, a novel marker for insulin resistance, and RHF is not well established in young adults. This study aimed to investigate the association between TyG index and RHF in Korean young adults.

Methods: Data were retrieved from the Korean National Health and Nutrition Examination Surveys (2010-2019). A total of 15,764 participants aged 19–39 years with normal kidney function were enrolled. The participants were divided into tertile based on TyG index [ln(fasting triglyceride [mg/dL] x fasting glucose [mg/dL]/2)]. RHF was defined as eGFR with residuals >90% percentile after adjusting for sex, age, weight, and height.

Results: The mean age of the study participants was 30.4 ± 6.1 years, and 43.8% were male. The mean levels of TyG index were 7.70 ± 0.25, 8.28 ± 0.15 and 9.07 ± 0.45 in tertile 1, 2, and 3 respectively. The prevalence of RHF was significantly higher tertile (9.1%, 10.0%, and 10.9%, respectively, P=0.03). When the association between TyG index and the risk for RHF was evaluated by multivariable logistic regression analysis, the higher tertiles showed increased risks for RHF compared to lowest tertile. (odds ratio [OR]1.24; 95% confidence interval [CI], 1.08-1.41, P=0.002 in tertile 2 and OR, 1.64; 95%CI, 1.41-1.90, P=0.001 in tertile 3). This association was consistent when TyG index was treated as continuous variable (OR, 1.53; 95% CI, 1.39-1.38; P<0.001). When subgroup analysis stratified by hypertension or diabetes were performed, no significant interactions were found, suggesting TyG index is an independent predictor for RHF regardless of hypertension or diabetes.

Conclusions: This study showed that higher TyG index is associated with increased risk of RHF in Korean young adults with normal kidney function. Longitudinal studies are need to investigate whether this association of TyG index levels associated RHF is an early risk factor for kidney injury in young adults.
PO2245
Screening for Early CKD in School Children in Kano, Nigeria
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Background: There has been an ongoing debate on the benefits of CKD screening in general especially as it relates to cost effectiveness and absolute relevance. However, screening for CKD in children will make a huge impact especially in low- and middle-income countries (LMIC) where treatment for End Stage CKD is not readily available due to high cost, shortage of skilled personnel and donor organs. This NIH/VECF Fogarty Funded research aimed to determine the burden of early CKD among school children in Kano, Nigeria.

Methods: The study screened 228 school children (5-15 years) within Kano metropolis for CKD from February 2020 to February 2021. Information of participants’ socio-demographic profile and medical history was obtained through questioning. Participants’ height, weight and blood pressure were measured. They also had their spot urine assessed for albumin creatinine ratio (ACR), and blood for serum creatinine and estimated glomerular filtration rate (eGFR). Participants with abnormal findings had a repeat assessment after three months for BP, ACR and eGFR.

Results: The median age of the children was 13.0 (11.1-14.0) years, with a male:female ratio of 1.1:1. Seventy-eight (34%) of the children (34%) had at least one abnormality in the form of hypertension, decreased eGFR (<90 ml/min/1.73m²) or increased ACR (>30 mg/g) at recruitment. Following re-assessment, 43 of the 78 children had persistent abnormal findings suggestive of early CKD (19%). Factors such as age, sex, type of school, parent’s education, history of family member with kidney disease, and nutritional status were not significantly associated with early CKD.

Conclusions: The outcome of this study indicates that a significant number of school children had persistent abnormal findings suggestive of early CKD. Thus, further emphasising the need for large scale CKD screening programmes in our setting. A long-term follow-up of these children will help determine the clinical significance of these findings and provide more information on the epidemiology of CKD. Abdullahi Mudi was supported by a VECD Global Health Fellowship, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW09337). The views expressed are solely those of the authors and do not necessarily represent the views of the NIH.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW09337).

PO2246
Advanced Liver Fibrosis Predicts CKD Development in Patients with Nonalcoholic Fatty Liver Disease
Chan-Young Jung, Hyung Woo Kim, Beom seok Kim. Yonsei University College of Medicine, Seoul, Seoul, Republic of Korea.

Background: Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated the association between liver fibrosis and the risk of incident CKD in patients with NAFLD.

Methods: A total of 5,983 participants with NAFLD (defined as controlled attenuation parameter (CAP) >222 db/m) but without CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The primary outcome was incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² or proteinuria (a1+ on dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Results: The mean age was 51.8 years and 3,756 (62.8%) participants were male. During the follow-up (mean follow-up of 3.0 years), 62 participants (1.0%) developed incident CKD. When stratified into TE-defined fibrosis stages, multivariable Cox models revealed that risk of incident CKD was 3.63-fold (95% CI, 1.64-8.06, P=0.001) higher in the F3-4 group (a9.5 KPa), compared to the F0 group (<5.5 KPa). During 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants (3.4%) experienced the secondary outcome, for which the F3-4 group had a 2.69-fold increased risk (95% CI, 1.70-4.27, P<0.001), compared to the F0 group.

Conclusions: In this large cohort of NAFLD patients without baseline CKD, advanced liver fibrosis measured by transient elastography was significantly associated with a higher risk of incident CKD.

PO2247
Association Between Rates of In-Hospital Decongestion Among Patients with Heart Failure with Reduced Ejection Fraction with Longer-Term Kidney Outcomes
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Background: Achievement of decongestion in acute heart failure (AHF) is associated with improved cardiovascular outcomes, but can be associated with acute declines in estimated glomerular filtration rate (eGFR). We aimed to examine whether rate of in-hospital decongestion is associated with longer term kidney function decline among patients with heart failure with reduced ejection fraction (HFrEF).

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between in-hospital change in assessments of volume overload, including b-type natriuretic peptide (BNP), N-terminal pro-type natriuretic peptide (N-proBNP) and clinical congestion score (0-12), as well as change in hemococentration including hematocrit, albumin and total protein with risk of incident chronic kidney disease (CKD) Stage≥4 (as defined by a new eGFR <30 ml/min/1.73m²) and eGFR decline of ≥40%.

Results: Among 3500 patients over 10-month follow-up, faster decreases in volume overload and more rapid increases in hemococentration were associated with decreased risk of incident CKD Stage≥4 and eGFR decline of ≥40%. In adjusted analyses, for every 6% faster decline in BNP per week, there was a 32% lower risk of both incident CKD Stage≥4 (HR=0.68, 95% CI 0.58, 0.87) and eGFR decline by ≥40% (HR=0.68 [0.57, 0.80]). For every 1% faster decrease per week in hematocrit, there was a lower risk for both incident CKD Stage≥4 (HR=0.73 [0.64, 0.84]) and eGFR decline by ≥40% (HR=0.82 [0.71, 0.95]), with results consistent for other biomarkers.

Conclusions: These results provide reassurance that more rapid rates of decongestion in patients with AHF do not increase the risk of adverse kidney outcomes in patients with HFrEF, and may in fact be associated with better kidney function in the long term. The ability to rapidly decongest may also serve as a valuable proxy for better kidney outcomes.

PO2248
Hearing Impairment Among Patients with CKD
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Background: Kidney and cochlear have similar physiologic mechanisms involving fluid and electrolytes. Impaired kidney function may affect cochlear function leading to hearing impairment (HI). Nevertheless, the association between chronic kidney disease (CKD) and hearing impairment is not clear. Moreover, the prevalence of HI among CKD patients has not been well-established.
PO2249

Genetic Determinants of Interleukin-6 Levels and Risk of ESRD
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Background: Multiple observational studies indicate an association between circulating levels of interleukin-6 (IL-6) and end-stage renal disease (ESRD). However, these studies are prone to confounding and reverse causation, limiting their utility in identifying causal relationships. Mendelian Randomization (MR) studies can provide evidence for causality by examining the relationship between genetically-determined biomarker levels and outcomes. We used MR to evaluate whether genetically predicted higher IL-6 levels are associated with the risk of ESRD.

Methods: We performed two-sample MR of the relationship between IL-6 and ESRD. We selected 5 single nucleotide polymorphisms (SNPs) robustly associated with higher IL-6 levels among Caucasians and 3,112 participants with serum samples collected at ARIC visit 1 (1987-1989) were included in this analysis. Starting with 318 individual metabolites, we formed clusters of metabolites using Netboost. We then examined longitudinal associations with ESRD and kidney failure using Cox regression. For significant clusters, we also assessed associations of component metabolites with the outcomes. Because the metabolomic profiling was performed in two studies, analyses were performed within each study and then meta-analyzed.

Results: There were 160 ESRD events and 357 kidney failure events during a median follow-up of 23.5 and 23.3 years, respectively. Overall, mean age was 53.5 years, 59.9% were women, and 61.4% were African American. Mean GFR was 107.5 (SD 16.7). We classified metabolites into 43 clusters. Four clusters were significantly associated with ESRD, and all were associated with kidney failure in a directionally consistent manner. Cluster 26 was primarily sugars involved in glycolysis and anaerobic metabolism. Cluster 5 included amino acids involved in liver metabolism using glutathione and gamma glutamyl transferases. Cluster 34 was an aggregation of lysolipids involved in creating phospholipid components of cell membranes. Significant component metabolites included: mannose and glucose from cluster 26; gamma-gluutamyl threonine, gamma-glutamyl threonine, and 5-enolepyrrole from cluster 5; and 6 lipids in the phospholipohene family from cluster 34. The association of mannose and glucose, higher levels of these metabolites were significantly related to lower risk of ESRD and kidney failure.

Conclusions: We identified several related metabolites associated with ESRD and kidney failure. Additional work is needed to determine whether the relationship is causal.

Funding: NIDDK Support

PO2250

Association Between Serum Metabolites and Adverse Renal Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study
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Background: Few metabolomic studies have characterized associations between metabolites and end-stage renal disease (ESRD) and kidney failure. Better characterization of the biological underpinnings may help identify at-risk individuals.

Methods: A total of 3,799 participants with serum samples collected at ARIC visit 1 (1987-1989) were included in this analysis. Starting with 318 individual metabolites, we formed clusters of metabolites using Netboost. We then examined longitudinal associations with ESRD and kidney failure using Cox regression. For significant clusters, we also assessed associations of component metabolites with the outcomes. Because the metabolomic profiling was performed in two studies, analyses were performed within each study and then meta-analyzed.

Results: The prevalence of speech frequency HI among patients with CKD was 74.8% among CKD stage 3, 75.9% among CKD stage 4, and 75.2% among CKD stage 5. After adjusting for age, sex, race, income, diabetes, hypertension, history of smoking, alcohol drinking, history of cardiovascular diseases, and loud noise exposure, CKD was significantly associated with higher odds of overall speech frequency HI (OR = 1.94, 95% CI [1.03, 3.64]; p < 0.04) and overall high-frequency HI (OR = 3.03, 95% CI [1.83, 5.02]; p < 0.001).

Conclusions: Nearly one-third of CKD patients have speech frequency HI and about 75% have high-frequency HI. Both speech frequency and high-frequency HI are common even in the early stage of CKD. CKD is independently associated with speech frequency and high frequency HI. Early screening and intervening on HI among CKD patients may enhance speech communication, prevent social isolation and improve quality of life.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Mean eGFR decreased with higher POx quartiles. eGFR modified the association of POx with CKD progression (P=0.01) and death (P=0.02). In participants with eGFR<45, higher POx quartiles were associated with CKD progression after adjusting for demographic factors, comorbidities, medications, lab values (including hemoglobin, serum albumin, urine protein-to-creatinine ratio), and eGFR (Q3 vs Q1: HR 2.97, 95% CI 1.12-3.82; Q4 vs Q1: HR 2.23, 95% CI 1.24-3.99). Higher POx was associated with death in participants with eGFR<45 after multivariable adjustment (Q4 vs Q1, HR 1.94, 95% CI 1.10-3.44). POx doubling was associated with a 34% increased risk of CKD progression and 28% increased risk of death (Table 1A). In those with eGFR<45, higher POx was associated with CKD progression after adjusting for demographic factors, comorbidities, medications, and lab values. Adjusting for eGFR attenuated these associations, with higher POx trending towards being protective of CKD progression. Associations of POx and death were not significant after adjusting for covariates and trended towards being protective after adjusting for eGFR (Table 1B). Sensitivity analyses adjusting for 24-hour urinary oxalate did not change these associations.

Conclusions: Higher plasma oxalate may be an independent risk factor for CKD progression/ESKD and death in persons with eGFR<45.

Funding: NIDDK Support, Private Foundation Support

PO2253

Associations of CKD Risk Factors and Longitudinal Changes in Urine Biomarkers of Kidney Tubules Among Women Living with HIV

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Background: Among women with HIV (WWH), urine biomarkers of tubule dysfunction and injury allow detection of antiretroviral toxicity and prediction of CKD risk and mortality. However, risk factors for changes in urine biomarkers are unclear.

Methods: We assessed traditional and infection-related CKD risk factors and measured 14 urine biomarkers at baseline and at follow-up (median 2.5 years) among WWH in the Women’s Intercagency HIV Study. We used similarly adjusted multivariable linear regression models to evaluate the associations of CKD risk factors with changes in biomarker levels concurrently.

Results: Of the 647 women in this analysis, 67% were Black, median age at baseline was 45 years and eGFR was 104 ml/min/1.73m². Each CKD risk factor associated with distinct changes in urine biomarkers (Figure). For example, baseline hemoglobin a1c (HbA1c) associated with worse tubular injury (higher interleukin-18 [IL-18]), proximal tubular reabsorptive dysfunction (higher alpha-1 microglobulin), tubular reserve (lower uromodulin) and heightened immune response to injury (higher chitinase-3-like protein [YKL-40]). Higher HbA1c at follow-up was associated with further worsening of tubular injury (higher kidney injury molecule-1 [KIM-1] and IL-18), and immune response to injury (higher YKL-40). Hepatitis C virus co-infection associated with worsening proximal tubular reabsorptive dysfunction (higher beta-2 microglobulin [β2m]), and immune response to injury (higher YKL-40), whereas HIV viremia associated with worsening markers of tubular and glomerular injury (higher KIM-1 and albumin, respectively).

Conclusions: CKD risk factors associated with unique patterns of biomarker changes among WWH, suggesting that longitudinal biomarker measurements may help in detecting and monitoring kidney disease in WWH.

Funding: NIDDK Support

PO2252

Relationship Between 24-Hour Urinary Oxalate and Incident CKD

Among Patients with and Without Underlying Gastrointestinal Disease

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Background: Hyperoxaluria may result from intake of high oxalate foods or enhanced intestinal absorption of dietary oxalate caused by gastrointestinal (GI) disorders with underlying malabsorption, including Crohn’s disease, short bowel syndrome, gastric bypass surgery, and chronic pancreatitis. Hyperoxaluria has been associated with negative outcomes, including kidney stones and chronic kidney disease (CKD), but larger studies are needed.

Methods: This is a longitudinal retrospective observational cohort study of patients in the US who have completed at least one 24-hr urine collection analyzed by a central laboratory during the study period of January 2013 through December 2020. Outcome and covariate data were drawn from a multi-source data cloud containing deterministically linked, de-identified, and centralized healthcare claims and electronic medical records (EMR) data. Malabsorption was defined by the presence of a relevant ICD 9/10 or CPT code. The association between categories of urine oxalate (UOx) and incident CKD was modeled using logistic regression.

Results: 762,537 individuals age ≥ 18y with at least one 24-hr urine collection were identified. At least 6 months of baseline and 6 months of follow-up data (median follow-up time: 36.7 months; IQR: 20.4, 56.0) were available for 447,958. Of these, N = 12,522 (2.8%) had an underlying malabsorptive condition preceding the index urine test. 426,896 individuals had no evidence of CKD at baseline and were eligible for analysis of incident CKD. After adjusting for baseline urine calcium, urine citrate, age, sex, race, BMI, tobacco use, hypertension, diabetes, malabsorption, and CVD, a significant association between baseline UOx and the development of incident CKD was observed. Compared with patients with UOx < 20 mg/d, the odds of developing incident CKD increased for 20-29 mg/d (OR: 1.22, 95% CI: 1.15, 1.30) through ≥ 80 mg/d (OR: 1.67, 95% CI: 1.51, 1.86) and was statistically significant for each UOx category.

Conclusions: In this large population of patients with hyperoxaluria, the risk of incident CKD increased with increasing 24-hr urine oxalate excretion. Future studies should examine whether reducing urine oxalate diminishes the risk of developing CKD.

Funding: Commercial Support - Synlogic Inc.
BMI, and percent change in estimated 24h urine Na were significant predictors of percent change in UPCR. The percent change in UPCR correlated with estimated 24h urine sodium on univariate linear regression (R² = 0.24, p < 0.01). We found that 68% of cases of UPCR rise also had estimated 24h urine Na increase, while 70% of patients with UPCR fall also had estimated 24h urine Na decrease.

Conclusions: Urine sodium and urine protein excretion correlated in patients with chronic kidney disease. Therefore, the role of dietary sodium as a potential influencing factor of urine protein excretion requires further examination.

PO2255
Liver Disease Is a Predictor of Recurrent Hyperkalemia
Elani Streja,1,2 Jui-Ting Hsiung,1,2 Abiy Agiro,1 Yasmin G. Brahmbhatt,1 Kerry Cooper,3 Kamyar Kalantar-Zadeh,2,4 V1 Long Beach Healthcare System, Long Beach, CA; 2University of California Irvine, Irvine, CA; 3AstraZeneca PLC, Cambridge, United Kingdom.

Background: Liver disease is a well-established predictor for recurrent hyperkalemia (HK) independent of mineralocorticoid receptor antagonist (MRA) therapy, which is a common treatment in this population. This study explores the relationship between liver disease and recurrent HK independent of MRA therapy and Renin Angiotensin System Inhibitors.

Methods: In a cohort of 9,894,683 US veterans that had at least one potassium measurement between 0.5-8 mEq/L during year 2004 and 2018, we identified 2,169,401 patients who had a HK event (sK >5.0 mEq/L) and complete data on covariables and examined the association of possible predictors of HK recurrence within 1 year after index HK event. Liver disease was defined according to the presence of mild, moderate, or severe liver disease ICD 9/10 codes using 1 inpatient or 2 outpatient records in one year prior to index HK event. HK recurrence is defined as the 3rd or later potassium measurement after index HK measurement subsequent to one or more normal (≤5 mEq/L) potassium measurement. Fine and Gray competing risk regression model was used to evaluate the association between liver disease and HK recurrence, where HK recurrence was the outcome and the competing event was all-cause mortality within 1 year after index HK occurrence. The model was adjusted for demographics, comorbid conditions, eGFR, RASi and MRA treatment and potassium supplementation.

Results: Among the 2,169,401 patients, 376,358 (17%) patients had HK recurrence within 1 year after index HK event. Out of 2,169,401 patients, 93,141 (4%) patients had liver disease within 1 year prior to index HK event and 26,846 (29%) of patients had HK recurrence within 1 year after index HK event. Patients with liver disease had a 39% higher risk of HK recurrence within 1 year after index HK event (hazard ratio [HR] [95% CI]: 1.39 [1.37, 1.42]) in the fully adjusted model and was the 2nd strongest predictor after diabetes. Compared to patients without liver disease, patients with liver disease were younger, more likely to be African American, and had a higher Charlson Comorbidity Index.

Conclusions: In US veterans, liver disease is a predictor of 1 year HK recurrence independently of RAASI therapy. Further studies are needed to understand the possible cause underlying this association.

Funding: Commercial Support - AstraZeneca

PO2256
Associations of Urinary and Dietary Sodium-to-Potassium Ratios with Albuminuria in Community-Dwelling Japanese Adults: A Cross-Sectional Study
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Background: Urinary sodium-to-potassium (Na/K) ratio is an indicator of dietary sodium intake and is associated with reduced kidney function. However, it is not known whether urinary Na/K ratio is also associated with albuminuria, the other key component of CKD, in community-dwelling adults.

Methods: We quantified the association of urinary Na/K ratio with albuminuria in 6,276 Japanese adults (age 40-97 years; 51.0% women) by using spot urine samples. Linear and logistic regression analyses were performed with adjustment for potential confounders. We also evaluated dietary Na/K ratio based on a food-frequecy questionnaire.

Results: Median values of urinary and dietary Na/K ratios were 2.70 (interquartile interval: 1.87, 3.83) and 1.50 (1.20, 1.84), respectively, with median albumin-to-creatinine ratio (ACR) of 11.0 (6.0, 24.0) mg/g and mean eGFR of 74.7 (SD 15.7) mL/min/1.73 m². In multivariable linear regression analysis, urinary Na/K ratio (per one-unit increment) was significantly associated with lower UNAK ratio and corresponding incidence rate was 14.0 (95% Confidence interval [CI], 12.9 to 15.3) per 1000 person-year. When the participants were categorized into quartiles according to UNAK ratio, age, sex and baseline eGFR adjusted hazard ratios (HR) (95% CI) for the Cox proportional hazard model were 0.76 (0.59-0.96), 0.89 (0.70-1.14), and 1.15 (0.91-1.46) from UNAK ratio quartile 1, 2, and 3, respectively as compared with the highest quartile. This finding was further confirmed in a real-world setting. Spline analysis showed that risk of albuminuria was increased more steeply up to 1.51, 1.12-2.04. Spline regression analysis show that HR increase more steeply up to the log-transformed UNAK ratio value of 0.023 [95% CI 0.008, 0.039] in Model 1 and 0.023 [95% CI 0.008, 0.039] in Model 2 in log transformed UNAK ratio, but there was no significant increase of risk after that.

Conclusions: Low Na/K ratio is significantly associated with a decreased risk of CKD development.

Funding: Government Support - Non-U.S.

PO2257
Urinary Sodium-to-Potassium Excretion Ratio Is Associated with Incident CKD in the General Population
Young Su Joo,1,2 Jong Hyun June,3 Hyung Woo Kim,1 Seung Hyok Han,1 Tae-Yeon Yoon,1 Shin-Woon Kang,2 Tuk Park,1 Yong Joo,1 Seong-Min Ha,1 Hae Won Lee,1 Joo Soo Park,1 Seung-Min Kwak,1 Nam Joo Han,3 Sung Jun Kang,1 Jong Hyun Yoon,1 Yoon Seung Hwa,4 Yoon Seung Hwa,5 Yoon Seung Hwa,6 Young Sub Ji,1,2 Jong Hyun June,3 Jong Seung Myung,7 Kyeong Seon Kang,1,2 Young Sub Ji,1,2 Jong Hyun June,3 Jong Seung Myung,7 Kyeong Seon Kang,1,2

Background: Previous study suggests that urinary sodium to potassium (UNAK) ratio is associated with cardiovascular event and mortality, but the association of incident chronic kidney disease (CKD) and UNAK ratio in a preserved kidney function adult showed conflict results.

Methods: Data: From the Korean Genome and Epidemiology, a prospective community-based cohort study were used to evaluate the between UNAK ratio and CKD development. 24 hour estimated sodium and potassium excretion amounts were calculated by a Kawasaki equation using spot urine potassium and sodium measurements. A total of 139 million of patients were analyzed and the primary outcome was defined as estimated glomerular filtration ratio (eGFR) <60 mL/min/1.73m² in a2 consecutive measurements during the follow-up period.

Results: The mean age was 52.1 ± 88 years and 47.5% were male. The mean estimated 24h urinary sodium excretion, potassium excretion, UNAK ratio were 4.9 (4.1-5.8) g/day, 2.1 (1.8-2.5) g/day, and 2.3 (1.9-2.7), respectively. During 37,950 person-year of follow-up (median 11.5 years), the primary outcome developed in 513 participants and corresponding incidence rate was 14.0 (95% Confidence interval [CI], 12.9 to 15.3) per 1000 person-year. When the participants were categorized into quartiles according to UNAK ratio, age, sex and baseline eGFR adjusted hazard ratios (HR) (95% CI) for the Cox proportional hazard model were 0.76 (0.59-0.96), 0.89 (0.70-1.14), and 1.15 (0.91-1.46) from UNAK ratio quartile 1, 2, and 3, respectively as compared with the highest quartile. This finding was further confirmed in a real-world setting. Spline analysis showed that risk of albuminuria was increased more steeply up to 1.51, 1.12-2.04. Spline regression analysis show that HR increase more steeply up to the log-transformed UNAK ratio value of 0.023 [95% CI 0.008, 0.039] in Model 1 and 0.023 [95% CI 0.008, 0.039] in Model 2 in log transformed UNAK ratio, but there was no significant increase of risk after that.

Conclusions: Low UNAK ratio is significantly associated with a decreased risk of CKD development.

Funding: Government Support - Non-U.S.
of surviving users continuing for over a year (Fig 1A). Mean serum K levels decreased after patiromer initiation and remained stable under treatment during follow-up (up to 180 days) (Fig 1B).

**Conclusions:** Most patients were not observed to discontinue patiromer prior to one year after initiation. Mean levels of serum K were lower after patiromer initiation and remained stable during the follow-up period.

**Funding:** Commercial Support - Vifor Pharmaceutical

**PO2259**

**Kidney Outcomes in Pediatric Non-Kidney Solid Organ Transplant Patients**

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**Background:** Acute Kidney Disease (AKD) is defined as impaired kidney function for < 90 days with or without an acute kidney injury (AKI) event. Adults with AKD have increased risk for progression to chronic kidney disease (CKD) and mortality. There are no data on the epidemiology of AKD in children after transplant. The aim of this study was to evaluate the incidence and risk factors for AKI, AKD and CKD at a large pediatric transplant center.

**Methods:** A retrospective chart review was done in children who underwent non-kidney solid organ transplant between 2011-2019 at UPMC Children’s Hospital of Pittsburgh. AKI and AKD are defined using the Kidney Disease Improving Global Outcomes criteria. AKD is defined as serum creatinine > 50% times baseline or eGFR < 60 ml/m2/1.73m2 or a decrease in eGFR by > 35% times baseline for > 7 days and up to 3 months. Patients with a new eGFR of < 60 ml/m2/1.73m2 persisting for > 3 months met criteria for CKD. Variables associated with AKI, AKD and CKD were analyzed.

**Results:** Among 338 patients 37.9% met criteria for severe AKI, 11.5% for AKD and 8% for a new diagnosis of CKD. Stage 3 AKI was independently associated with AKD (OR: 4.10; 95% CI: 1.64-10.25), AKD but not severe AKI was associated with new onset CKD (Table 1). There was a dose dependent relationship between nephrotoxic medication use and incidence of AKD (Figure 1).

**Conclusions:** In conclusion, children with AKD after transplant are particularly vulnerable to developing CKD and there are modifiable risk factors that could decrease the risk of progression of AKI to AKD and CKD in this population.

Multivariable logistic regression of risk factors for CKD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.00-1.099</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender</td>
<td>2.67 (1.06-7.13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Race</td>
<td>2.35 (0.97-5.77)</td>
<td>0.08</td>
</tr>
<tr>
<td>Severe AKI</td>
<td>11.04 (3.02-42.79)</td>
<td>0.09</td>
</tr>
<tr>
<td>All AKI</td>
<td>1.58 (0.48-5.40)</td>
<td>0.49</td>
</tr>
<tr>
<td>CKD</td>
<td>20.45 (7.53-57.77)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**PO2260**

**Cardiovascular Outcomes in Pediatric CKD: A CKD Study**

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**Background:** Cardiovascular Disease (CVD) poses high risk to Chronic Kidney Disease (CKD) pediatric patients with existing literature noting decreased mortality and other comorbidities. Here, we use the Chronic Kidney Disease in Children Cohort Study (CKiD), a prospective cohort study of pediatric renal cystic patients, to assess CVD parameters in this vulnerable population.

**Methods:** We performed control-match analysis of CKD patients with prevalent renal cystic disease (PKD, MCKD, BOR) compared to a group of aplastic/dysplastic/hypoplastic kidney patients or those with obstructive uropathy. Variables were normalized using the Kolmogorov-Smirnov test; categorical variables were summarized as percentages while continuous variables as medians and inter-quartile ranges. Univariate associations were tested using chi-square statistic or Fischer exact test for categorical variables and Mann-Whitney U test for continuous variables.

**Results:** 41 patients in the renal cystic group were compared to 294 patients in the non-renal non-cystic group. Renal cystic patients demonstrated statistically significant increases in cystatin-C with no difference in iFGF or serum creatinine. Blood pressure was decreased [103.97-112] vs. [107.09-115] mmHg; p=0.004) in the renal cystic group but cardiac parameters of ascending aortic stiffness [3.1 (2.11 - 5.21)] vs. 2.53 (1.87 - 3.56); p=0.001] and incidence of left-ventricular hypertrophy (LVH) [12 (15.2%) vs. 44 (8.3%); p=0.049] was increased.

**Conclusions:** CVD mortality is the primary cause of death in patients with CKD, especially ADPKD. Previous literature conceptualized link between renal cystic disease and hypertension leading to poorer CVD outcomes however our analyses show this is an incomplete picture with almost 50% higher incidence of LVH but lower blood pressure in renal cystic group compared to other CKD pediatric patients. This suggests a need for further exploration of cardiac remodeling and structural changes to improve the understanding of CVD development in renal cystic pediatric patients.

**PO2261**

**Biopsy-Proven CKD Etiology and Outcomes: The CKD Japan Cohort (CKD-JAC) Study**

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**Background:** The KDIGO guidelines advocated cause-GFR-albuminuria (CGA) classification for predicting outcomes. However, the depth of data exists supporting the use of the cause of chronic kidney disease (CKD). This study aimed to address how to incorporate prior biopsy-proven diagnosis in predicting outcomes.

**Methods:** We compared end-stage kidney disease (ESKD) and all-cause death before ESKD among various biopsy-proven diagnoses (n = 778) in Analysis A. In Analysis B, the same outcomes were compared among biopsy-proven diabetic nephropathy (DN), biopsy-proven other diseases, and no biopsy in those with a history of diabetes mellitus (n = 1117).

**Results:** In analysis A, adding biopsy-proven diagnoses to GFR-albuminuria (GA) classification significantly improved both net reclassification improvement and integrated discrimination improvement to predict the 8-year incidence of ESKD and all-cause death. Fine-Gray (FG) models with ESKD as a competing event showed significantly higher subdistribution hazard ratios (SHRs) for all-cause death in nephrosclerosis (4.12 [1.11–15.2]), focal segmental glomerulosclerosis (3.77 [1.09–13.1]), and membranous nephropathy (MN) (2.91 [1.02–8.30]) as compared to IgA nephropathy, while Cox model failed to show significant associations. Crescentic glomerulonephritis had the highest risk of all-cause death (sHR 5.90 [2.05–17.1]). MN had a significantly lower risk of ESKD than IgA nephropathy (sHR 0.45, [95% Confidence interval:0.24–0.84]). In analysis B, biopsy-proven other diseases had a lower risk of ESKD as compared to biopsy-proven DN in FG model with death as a competing event (sHR 0.62 [0.39–0.97]).

**Conclusions:** The biopsy-proven cause of CKD is of great value in predicting outcomes in CKD adjusting for GA classification.

**Funding:** Commercial Support - Kyowa-Kirin company

Association between nephrotoxic medication use and AKD
PO2262

Ideal Cardiovascular Health and Risk for Incident CKD: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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Background: Prior studies have reported that measures of ideal cardiovascular health influence the risk of developing chronic kidney disease (CKD). However, U.S. Hispanic/Latino adults were not well represented in these studies.

Methods: We analyzed data from 8,770 U.S. Hispanic/Latino adults aged 18-64 years enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) who completed a baseline (2008-2011) and a follow-up (2014-2017) visit and did not have CKD at baseline (estimated glomerular filtration rate [eGFR] ≥ 60 ml/min/1.73m²) and were not in prevalent CKD at baseline. After a median follow-up of 5.9 years, there were 598 incident albuminuria events, and 201 low eGFR events. Compared with the presence of <4 ideal factors, ≥4 ideal health factors was associated with lower risk for incident albuminuria but there was no association with incident eGFR (Table).

Conclusions: Among U.S. Hispanic/Latino adults, the presence of a higher number of ideal health factors was associated with a lower risk of incident albuminuria. These findings may have implications for public health strategies for CKD prevention in this population.

*Adjusted for center, age, sex, background, education, eGFR, and log(UACR)

PO2263

Inflammatory Biomarkers and Proteinuria Progression in CKD Patients: The CRIC Study

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Background: Proteinuria progression is considered a surrogate endpoint for CKD progression. We studied prospective association of inflammatory biomarkers with proteinuria progression in the Chronic Renal Insufficiency Cohort (CRIC) Study participants.

Methods: The CRIC Study recruited 3939 CKD patients in the U.S. After excluding those without urine protein measures at baseline or follow-up and those with missing covariates at baseline, 3177 patients were included in this analysis. Proteinuria progression was defined as a ≥30% increase in urine protein-to-creatinine ratio (UPCR) from baseline and UPCR ≥150 mg/g at follow-up visits. Incident proteinuria was defined as UPCR ≥75 mg/g at baseline and UPCR ≥150 mg/g at follow-up visits. Cox proportional hazards models were used to examine multivariable association of inflammatory biomarkers with proteinuria progression and incidence, adjusting for age, sex, race, current smoking, body mass index, systolic blood pressure, total cholesterol, hemoglobin A1C, eGFR, baseline UPCR, and use of ACE-Inhibitors, statins, and aspirin.

Results: Over a mean follow-up of 6.6 years, 1478 participants developed proteinuria progression and 625 participants developed proteinuria. Multivariable-adjusted hazard ratios (95% confidence intervals [CI]) of proteinuria progression for the highest quartile vs. lowest quartile of inflammatory biomarker levels were 1.36 (1.01–1.86; P=0.04) for fibrinogen, 1.21 (1.03-1.43; P<0.001) for interleukin-6 (IL-6), 1.54 (1.30-1.81; P<0.0001) for tumor necrosis factor-α (TNF-α), and 1.22 (1.04-1.42; P=0.01) for CXCL12. Among 1635 patients without baseline proteinuria, similar relationships of fibrinogen, IL-6, TNF-α and CXCL12 with incident proteinuria were identified. C-reactive protein, white blood cells, IL-1β, IL-1 receptor antagonist, fetuin-A, transforming growth factor-β, and fractalkine were not significantly associated with proteinuria progression or incidence.

Conclusions: Our findings suggest that higher levels of fibrinogen, IL-6, TNF-α, and CXCL12 are independently associated with proteinuria progression and incidence. Future studies may test whether targeting specific inflammatory pathways will improve proteinuria and reduce CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences (NIGMS)

PO2264

Racial Disparities in Progression to ESRD and Mortality in Rural vs. Urban Veterans

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Background: Little is known about how race and rurality interact to influence progression of CKD to ESRD and mortality in CKD patients.

Methods: We analyzed a national cohort (n=915,039) of veterans with CKD (eGFR ≤ 60 on two or more outpatient serum creatinine >60 days apart) who received care from 1/1/2010-12/31/2015 and who had information on demographics, comorbidities, and residence coding available. ESRD data was obtained by linkage to USRDS. Cox linear regression models were used to relate rural and urban residence defined by RUCA codes with time to incidence of ESRD, as well as time to all-cause mortality. The models were adjusted for age, gender, and comorbidities. The full cohort was examined as well as two subgroups divided by race. Hazard ratios were calculated using the urban (RUCA 1.0 & 1.1) veterans within the full cohort or each subgroup as a reference.

Results: When compared to urban veterans, veterans who reside in rural regions had lower risk of ESRD (HR 0.89, 95% CI 0.85-0.91) but had a slightly higher risk of mortality (HR 1.03, 95% CI 1.02-1.03). Within race subgroups, White rural veterans had lower risk of ESRD compared to White urban veterans (HR 0.88, 95% CI 0.85-0.91) but not in Black versus Black urban veterans (HR 0.99, 95% CI 0.93-1.05). While rural White veterans had slightly higher risk of mortality compared to urban White veterans (HR 1.02, 95% CI 1.01-1.02), the difference in mortality between rural and urban veterans was much larger in the Black subgroup (HR 1.11, 95% CI 1.08-1.14).

Conclusions: Examination of CKD patients cared for by the VA reveals an interaction between race and rurality in which mortality is increased in rural Black veterans with CKD. Interventions to improve preESRD care in rural Black veterans are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support
PO2265
Trends in Prevalence of Comorbid Conditions at Onset of CKD Among US Veterans with Incident CKD, 2004-2018
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Background: Many comorbid conditions are strong risk factors for adverse outcomes in people with CKD. We examined trends in prevalence of major comorbidities at CKD onset in the US Veterans Health Administration (VHA).

Methods: Incident CKD was defined as the first time the estimated glomerular filtration rate (eGFR) decreased to < 60 mL/min/1.73 m2 for ≥ 3 months. We excluded veterans recorded in the VHA for < 2 years prior to the first eGFR < 60, or with CKD stage ≥ 4 when first identified. We identified 15 comorbidities at CKD onset using ICD-9/ICD-10 codes during the 2 years before and 6 months after CKD onset and calculated the Charlson comorbidity index (CCI), a composite score of total disease burden.

Results: The cohort included 892,005 veterans with new-onset CKD between 2004 and 2018. The mean age (72 years), eGFR (52 mL/min/1.73 m2), and body mass index (30 kg/m2) at CKD onset were similar in 2004 and 2018. Among the 8 comorbidities with ≥ 20% prevalence, sex, LDL-cholesterol, HbA1c, systolic blood pressure, diabetes duration and BMI of patients with a CCI ≥ 6 increased from 9% in 2004 to 14% in 2018.

Conclusions: In US veterans, obesity, depression and the CCI score have significantly increased at CKD onset over the recent 15 years, underscoring the importance of a multifaceted approach to management of CKD and its risk factors.

Funding: NIDDK Support, Other U.S. Government Support

PO2266
Association Between Cardiac Autonomic Function and Coronary Artery Calcification in Persons with Type 2 Diabetes with and Without CKD
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Background: Cardiac autonomic neuropathy and cardiovascular disease are concomitant complications to diabetes but the link between these complications are largely unknown, especially in relation to kidney function. We examined the association between measures of cardiac autonomic function and coronary artery calcification (CACS) in persons with type 2 diabetes stratified by presence of chronic kidney disease (CKD).

Methods: Post-hoc analysis of baseline data from a randomized clinical trial including 84 persons with type 2 diabetes. Cardiac autonomic function was evaluated using heart rate variability (HRV) indices and cardiovascular autonomic reflex tests (CARTs). Lower response in CARTs and HRV measures were taken as indicators of impaired cardiac autonomic function. CT based CACS was calculated using Agatston method.

Results: The participants had a mean age of 64.7 (SD 7.8) years, 15% were women, mean eGFR was 83.5 (SD 16.2) ml/min/1.73 m2, median albuminuria creatinine ratio 5.5 [Q3R 3.5 – 11.8] mg/g and 10 (11.5%) had CKD (eGFR < 60 ml/min/1.73 m2). In persons without CKD, a higher CACS was associated with a lower 30-to-15 ratio (-1.27, SE: 0.33, p < 0.0001), E-to-I ratio (1.33, SE:0.32, p < 0.0001), standard deviation of normal-to-normal intervals (-0.73 ms, SE:0.34, p=0.03), high frequency power (-0.49 ms2, SE:0.24, p=0.045) and total power (-0.86 ms2, SE:0.33, p=0.01). All these associations remained significant after adjustment for age, heart rate (only for HRV measures), sex, LD, BMI, HbA1c, c-systolic blood pressure, diabetes duration and weight (except for standard deviation of normal-to-normal intervals and high frequency). In persons with CKD, no significant associations were demonstrated between measures of cardiac autonomic neuropathy and CACS.

Conclusions: In persons with type 2 diabetes but without CKD, we demonstrated an association between impaired cardiac autonomic function and higher coronary artery calcification. This association could not be demonstrated in persons with CKD.

Funding: Government Support - Non-U.S.

PO2267
Characterization of Metabolome-Wide Biochemicals Associated with Kidney Function
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Background: Chronic kidney disease (CKD) is a global public health problem. Identifying sensitive filtration biomarkers is a key diagnostic value contributing to an understanding of CKD at the molecular level. A metabolomics study indicated a snapshot of the biochemical activity of the human body at a particular time in the progression of CKD. This metabolome-wide study verified whether blood metabolite profiles are significantly different in different stages of CKD and characterized potential markers to assess kidney function in Chinese population.

Methods: An analysis of plasma and serum metabolites using ultrahigh-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was performed on 198 participants (55 serum samples and 145 plasma samples) based on their measured GFR (by iohexol plasma clearance).

Results: A large number of metabolomics related to the mGFR were selected as the top 30 metabolites by the random forest method, and we found 15 amino acids, 8 nucleotides, and 2 carbohydrates strongly related to kidney function in the combined group (plasma and serum). Thirteen amino acids, 9 nucleotides, and 3 carbohydrates were identified in the plasma group, while 13 amino acids, 7 nucleotides, and 3 carbohydrates were found in the serum group. We observed that 10 of the top 15 ranked metabolites were concordant between the plasma and serum groups. Major differences in metabolite profiles with increasing stage of CKD were observed.

Conclusions: Our study identified 6 novel and potential metabolites that reproducibly strongly associate with mGFR, including pseudouridine, C-glycosyltryptophan, N-acetylanaline, myo-inositol, and N-acetylcarnosine. However, pseudouridine may be an ideal biomarker that is nondependent on race. Specifically, a potential negative biomarker of kidney disease may be 1,5-anhydroglucitol (1,5-AG).
Future studies will utilize the potential 3-5 novel biomarkers in estimating the glomerular filtration rate without race interference.

Funding: Government Support - Non-U.S.

PO2268
Lipid Accumulation Product Index and CKD
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Background: Obesity, a well-known risk factor for chronic kidney disease (CKD), is generally assessed using body mass index (BMI). However, because BMI does not take body composition into account, it may not reflect the metabolic abnormalities associated with obesity. Recently, lipid accumulation product index (LAP) has been proposed to effectively recognize metabolic syndrome. Therefore, the association between LAP and risk of incident CKD was investigated in a general population cohort.

Methods: A total of 180,268 subjects without CKD, who participated in the Korean Genome and Epidemiology Study from 2001 to 2018, were analyzed. LAP was calculated as [waist(cm)-65] × triglyceride(mmol/l) for males and [waist(cm)-58] × triglyceride(mmol/l) for females. The association between LAP and risk of incident CKD was investigated in a general population cohort.

Results: We found that with increasing LAP, the risk of incident CKD increased. For males, the adjusted hazard ratios (95% confidence intervals) were 1.0 (referent category) for LAP < 3, 1.1 (1.0-1.2) for 3 ≤ LAP < 4, 1.2 (1.0-1.4) for 4 ≤ LAP < 5, 1.3 (1.1-1.6) for 5 ≤ LAP < 6, and 1.4 (1.2-1.7) for LAP ≥ 6. For females, the adjusted hazard ratios (95% confidence intervals) were 1.0 (referent category) for LAP < 2, 1.1 (1.0-1.2) for 2 ≤ LAP < 3, 1.2 (1.0-1.4) for 3 ≤ LAP < 4, 1.3 (1.1-1.7) for 4 ≤ LAP < 5, and 1.5 (1.3-1.8) for LAP ≥ 5.

Conclusions: The LAP is associated with the risk of incident CKD in both sexes. This study suggests that the LAP is a potential biomarker that can be utilized in predicting the risk of incident CKD. The results indicate the importance of considering body composition in the risk assessment of CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
in CKD odds ratio (OR) 1.47; 95% CI, 1.35-1.61; P<0.001). When stratified into tertiles, the risk of CKD prevalence was significantly higher in the highest tertile (OR 2.05; 95% CI, 1.72-2.45; P<0.001), when compared to the lowest tertile. During a mean follow-up of 182 months, CKD occurred in 720 (8.5%) participants. In the multivariable Cox analysis, LAP was significantly related with incident CKD risk (per 1-log LAP, HR 1.20; 95% CI, 1.13-1.27; P<0.001). The risk of incident CKD was significantly higher in the highest tertile (HR 1.48; 95% CI, 1.32-1.65) than the lowest tertile.

Conclusions: Increase in LAP was associated with higher prevalence of CKD and elevated risk of incident CKD.

Figure 1. Cumulative incidence curve for incident chronic kidney disease according to lipid accumulation product index.

PO2269
Comparison of Two Immunoassay Technologies for Plasma Biomarker Measurement
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Background: Anti-double-stranded DNA (anti-dsDNA) antibodies in autoimmune diseases such as systemic lupus erythematosus (SLE) may interfere with immunoassay technologies that use oligonucleotide-based antibodies (Olink) or aptamers (SomaScan). In this study, we compare measurements of plasma kidney injury molecule-1 (KIM-1), a well-known marker of tubular injury, across two different immunoassay technologies in patients with and without SLE.

Methods: We measured plasma KIM-1 levels in 444 individuals enrolled into a prospective, observational cohort study of patients with chronic kidney disease using microbead-based sandwich ELISA and the proximity extension assay (PEA, Olink). The PEA uses oligonucleotide-labeled antibodies that bind to the target protein. We investigated differences in plasma KIM-1 measurements between the two assays in individuals with SLE (n=68) and individuals with other diseases than SLE (n=376) using Bland-Altman plots and Spearman correlation coefficients.

Results: Mean eGFR was 85.2±37 and 52.3±33 ml/min/1.73m² and the median proteinuria (IQR) was 1.5 (0.7, 3.2) and 1.7 (0.4, 4.2) g/g creatinine in individuals with and without SLE, respectively. The correlation between paired plasma KIM-1 measurements from both assays was 0.7 (p<0.001) in individuals with SLE and 0.9 (p=0.001) in individuals with other diseases than SLE (Figure 1A). The Bland-Altman plots show the bias between the mean differences in plasma KIM-1 in individuals with and without SLE, indicating that the bias in measurements was significantly greater in those with than without SLE (2.8 vs. -3 units, p=0.008, Figure 1B).

Conclusions: Anti-dsDNA antibodies in SLE may interfere with measurements by oligonucleotide-labeled antibodies.

Funding: NIDDK Support

Figure 1.

PO2270
Associations Between eGFR and Brain Atrophy
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Background: The associations between estimated glomerular filtration rate (eGFR) and both cognitive decline and brain atrophy have been less studied in elderly with kidney disease. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is an NIH funded multicenter observational study characterizing progression of dementia in the elderly. Using the ADNI data, we analyzed the association between eGFR and brain volume.

Methods: We used multiple linear regression model to determine the association between eGFR and normalized (brain region divided by intracranial volume) whole brain and hippocampal volume (primary outcomes) and entorhinal cortex, and middle temporal gyrus volumes (secondary outcomes) as determined by brain MRI.

Results: Mean age of the 1596 ADNI participants was 74 ± 7 years; 53% had mild cognitive impairment (MCI), and 19% had dementia. 27% had eGFR <60 ml/min/1.73m². Participants with lower eGFR were older, had a higher prevalence of diabetes, while increasing age, and female sex were associated with lower brain volumes, lower eGFR was not (table 1). The results persisted in sub analyses divided by tertiles of age in participants with normal cognition, MCI, or dementia.

Conclusions: Low eGFR is associated with lower brain atrophy in the ADNI participants with mild-moderate reduction in eGFR.

Funding: Other NIH Support - NIA

Multiple linear regression model predicting brain volumes.

PO2271
Correlation of Silent Brain Infarction with the Metabolic Abnormality of CKD Stage 3-5 (Nondiabetic) Patients
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Background: Silent brain infarction (SBI) is a hidden comorbidity, mostly unrecognized in CKD patients which increases the risk of symptomatic stroke, dementia and mortality. Metabolic abnormalities are also associated with the progression of CKD. The relationship between SBI and chronic kidney disease (CKD) is unknown. It is supposed that SBI will predict the progression of diseases processes in CKD patients.

Methods: This is a cross-sectional study. A total of 115 subjects were enrolled in this study. 85 patients of CKD stage 3-5 (non diabetic) who have no neurological symptoms suggesting stroke were considered as group I and Group-II were 30 healthy controlI.

Results: The proportion of Silent Brain Infarction is 52.9% in CKD patients. SBI was found in 45(52.9%) patients in group I and 4(13.3%) in group II which was significant (p<0.05). The proportion of SBI was also increased in higher CKD stages. (stage-3.8.9%; stage-4.3.56%; stage-5ND:55.6%). In a multivariate logistic regression analysis CKD had independent relationship with SBI along with serum phosphate and parathyroid hormone level (CKD had Odds ratio (OR)=1.847 (95.0% CI 0.064 to 53.319), serum PO₄ had OR=0.958 (95.0% CI. 0.885 to 1.038) and serum PTH had OR=0.996 (95.0% CI. 0.993 to 1.000). Spearman rank correlation coefficient test showed positive correlation between SBI and serum P0₄ level (r=0.416, p=0.001) and serum PTH level (r=0.405, p=0.001) separately.

Conclusions: The proportion of SBI in CKD stage 3-5 (non diabetic) patients is high which is 52.9% and serum PO₄ and serum PTH level have positive correlation with the development of SBI in CKD stage 3-5 (non diabetic) patients.

Funding: Clinical Revenue Support

PO2272
Risk Factors for Incident Pruritus in Patients with CKD Not on Dialysis
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Background: Pruritus is common in patients with CKD not on dialysis, but its incidence and risk factors have not been rigorously evaluated.

Methods: Using data from the Chronic Renal Insuﬃciency Cohort (CRIC) study, we identiﬁed 2,164 participants that were pruritus free at baseline. Pruritus was assessed for age, sex, race, ethnicity, diabetes, smoking status, and opioid use to analyze the association of pruritus with baseline estimated GFR, categorized as <30, 30 to <45, 45 to <60, and ≥60 ml/min/1.73 m². In an exploratory analysis, markers of bone-mineral metabolism and inﬂammation, possible mediators of the association between eGFR and pruritus, were added to the models to evaluate their association with risk of pruritus.
Results: The mean age of participants was 58 years, 43% were women, and 43% Black. During a median follow-up of 6.0 years, 684 participants developed moderate-to-severe pruritus, with an overall unadjusted incidence rate of 4.6 per 100 person-years. The 5-year unadjusted cumulative incidence of pruritus was: overall 21%, eGFR ≥60 18%, eGFR 45 to <60 20%, eGFR 30 to <45 24%, and eGFR <30 20%. In the fully adjusted model, compared to eGFR ≥60, an eGFR of 30-45 was associated with a 39% (95% CI 1.08 – 1.80) higher risk of pruritus, and an eGFR <30 was associated with a 56% (95% CI 1.15 – 2.11) higher risk of pruritus (Figure 1). Female sex, diabetes, current smoking, and opioid use were associated with increased risk of pruritus, independent of eGFR. Notably, serum albumin and C-reactive protein were independently associated with pruritus, whereas calcium, phosphorus, and parathyroid hormone were not.

Conclusions: A significant proportion of patients with CKD develop pruritus, even at modestly reduced eGFR ≤ 45 mL/min/1.73 m². Careful assessment and management of pruritus should be considered as a part of routine CKD care.

Funding: NIDDK Support

Adjusted cumulative incidence of pruritus by eGFR in the CRIC study

PO2273
Subtle Changes in Uremic Symptoms with CKD Progression
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Background: Uremic symptoms are a major contributor to symptom burden in CKD and related to lower quality of life. However, factors associated with uremic symptom progression have not been rigorously examined.

Methods: We included 3,504 participants with CKD not on dialysis from the Chronic Renal Insufficiency Cohort (CRIC) study with at least two assessments of estimated GFR (eGFR) and uremic symptoms. The uremic symptoms fatigue, anorexia, and pruritus were assessed annually by the Kidney Disease Quality of Life instrument. Responses were transformed to a scale from 0-100, with lower scores indicating worse symptom severity. We used multivariate linear mixed effects models with random intercepts and random slopes to estimate the association between eGFR change and the change in uremic symptoms over time.

Results: The mean age of participants was 58 years, 43% were women, 41% Black, and the mean eGFR at baseline was 45 mL/min/1.73 m². Over a median follow-up of 7 years (IQR 3-11), the average annual decline in eGFR was -1.3 mL/min/1.73m²/year. The average annual change in the symptom scores for fatigue, anorexia, and pruritus were -0.27 (95% CI: -0.35, -0.19), -0.26 (95% CI: -0.33, -0.19), and -0.49 (95% CI: -0.59, -0.39), respectively. A 10-unit change in eGFR was significantly associated with worsening fatigue, anorexia, and pruritus (Table 1). The association was stronger for those with eGFR <30 than those with higher eGFR.

Conclusions: Decreasing kidney function is associated with worsening fatigue, anorexia, and pruritus; however, the absolute change in symptom severity scores is small and unlikely to be clinically meaningful. Regular symptom assessment should be incorporated into routine CKD care; however, caution should be used when attributing large changes in symptom severity solely to changes in the level of kidney function.

Funding: NIDDK Support

Change in symptom score per 10-unit decrease in eGFR

PO2274
Conservative Kidney Management Practice Patterns in the United States: A CKDopps Analysis
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Background: Conservative kidney management (CKM) of kidney failure is an important treatment option for many patients. However, its availability in the United States (US) is not well described. We describe CKM resources and provider practice patterns in US Chronic Kidney Disease (CKD) clinics.

Methods: Cross sectional analysis of provider surveys (n=22) from unique clinics in the US from the CKD Outcomes and Practice Patterns Study (CKDopps) collected between 2014-2017.

Results: Only eight (36%) providers reported involving palliative care in planning for and educating patients about kidney failure. A majority (59%) were extremely comfortable discussing CKM and nearly 100% typically discussed CKM as a treatment option. Nearly all (95%) reported their clinics had the ability to routinely deliver CKM, but only one had a CKM protocol or guideline, and none offered a specific CKM clinic. Most providers said their clinics used the word “conservative” to describe CKM, with 24% choosing “palliative” or “supportive” terminology. Regardless of involvement of PC, most providers estimated that 5% of their patients with or approaching kidney failure were managed with CKM. Patient preference, functional status, frailty, and comorbidities were the most important factors influencing provider decisions in contemplating the suitability of CKM for patients. (Figure 1)

Conclusions: Most providers report feeling comfortable discussing CKM, yet almost no clinics report resources or dedicated infrastructure for CKM delivery. Despite reported high frequency of discussing CKM, few patients were described as choosing this treatment pathway. Factors that influence consideration of CKM are consistent with elements that generally influence well-informed geriatric and end-of-life care. Efforts to improve assessment of those elements may allow for more informed recommendations of CKM.

Funding: NIDDK Support

Factors influencing providers to consider conservative kidney management

PO2275
Association Between Monocyte Counts and All-Cause Mortality in Patients with CKD
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Background: In the general population, monocyte counts are strongly associated with a higher risk of all-cause mortality. However, little is known whether this association translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if monocyte counts are associated with the risk of all-cause mortality in patients with non-dialysis CKD who participated in the Chronic Renal Insufficiency Cohort (CRIC) observational study.

Methods: Patients were divided in tertiles according to their monocyte counts at baseline, and survival analysis was performed using Kaplan-Meier curve with statistical comparison by the log rank test. Cox models with time interaction effects were used to examine the association between monocyte counts and all-cause mortality.

Results: Among the 3,939 CRIC participants, a total of 3,391 participants (1,838 males and 1,553 females) were included in the final analytic cohort, with a mean ± SD eGFR of 45 ± 15 mL/min/1.73 m² and age of 58 ± 11 years. Participants in the highest tertile of monocyte count had a lower rate of survival than those in the lowest tertile (P<0.001, Figure). At follow-up time of 5 years, there was a 39% higher risk for all-cause mortality (95% CI: 22-59%) with every 2-fold increase of monocyte count after adjusting for age, sex, race, clinic site, traditional cardiovascular risk factors, markers of kidney disease, and C-reactive protein (fully adjusted model).

Funding: NIDDK Support

*Model adjusted for age, gender, race/ethnicity, baseline symptom score, BMI, employment, cancer history, total number of medications, ACEI/ARB, NSAIDs, antidepressants, opioids, gabapentin, and time.

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PO2276
Kidney Disease and Longitudinal Changes in Muscle Strength in Older Adults
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Background: Persons with chronic kidney disease (CKD) experience lower physical function and increased risk of disability, both of which have strong prognostic importance for poor clinical outcomes. To date, functional status studies in populations with CKD have focused on physical activity and/or individuals with end-stage kidney disease, and have largely neglected measures of muscle strength, especially among those with non-dialysis dependent CKD.

Methods: Participants were from the Health, Aging and Body Composition Study, a longitudinal cohort focused on functional decline in adults aged 70-79 years at baseline. Kidney function was defined by estimated glomerular filtration rate (eGFR) using the CKD-EPI Cystatin C Equation at each available visit (up to 5) during 10 years of follow up. Participants were grouped based upon their longitudinal eGFR: no CKD (eGFR ≥ 60 mL/min/1.73 m^2), prevalent CKD (baseline eGFR < 60 mL/min/1.73 m^2), and incident CKD (baseline eGFR ≥ 60 but < 60 mL/min/1.73 m^2 during follow up). Grip and quadriceps strength were also assessed longitudinally (8 and 6 visits, respectively). Linear mixed models stratified by sex tested associations between kidney function groups and grip and quadriceps strength over time.

Results: Of the 2,630 participants with median age 73 years, 64.9% had no CKD, 23.4% had prevalent CKD, and 11.7% developed incident CKD. At baseline, men and women without CKD had higher unadjusted grip and quadriceps strength compared to those with CKD. In adjusted linear mixed models for grip strength, men with CKD had faster decline over time, compared to men without CKD (Table). For women, changes in grip strength were not different across kidney function groups. In adjusted models of quadriceps strength over time, there were no differences among kidney function groups.

Conclusions: Men with CKD had faster decline in grip strength compared to those without CKD. Future studies can determine if recognizing decreased muscle strength and intervening can change this functional trajectory among those with CKD.

Funding: NIDDK Support

PO2277
Health-Related Quality of Life in Patients with Inflammation and Non-Dialysis-Dependent CKD
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Background: Inflammation is common in chronic kidney disease (CKD) and can affect treatment of anemia, which is a common complication of CKD. Both inflammation and anemia in CKD have been linked with poor health-related quality of life (HRQoL), though evidence is limited. We aimed to assess the association between inflammation and HRQoL in patients with non-dialysis dependent CKD (NDD-CKD).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a point-in-time survey of physicians and their patients with CKD (stage 3-5D) collected in the United States in 2018. Patients were also invited to complete a questionnaire which included subjective assessment of the impact of CKD, as well as the Kidney Disease Quality of Life-36 questionnaire (KDQoL-36). Patients with NDD-CKD who filled out the KDQoL-36 were included in this analysis. Inflammation was defined as C-reactive protein ≥ 4.9 mg/L, ferritin ≥ 700 ng/mL, or albumin ≤ 3.6 g/L. T-tests were conducted to assess differences in KDQoL-36 scores between patients with and without inflammation.

Results: Inflammation was present in 136/491 (28%) patients. Mean KDQoL-36 scores were lower with inflammation compared to no inflammation in all 5 domains (all p<0.05; Table 1). Most differences in KDQoL scores between patients with and without inflammation exceeded the distribution-based minimal clinically important difference (MCID).

Conclusions: We found that patients with inflammation in NDD-CKD reported poorer HRQoL compared with those without. Reducing inflammation in CKD may improve HRQoL.

Funding: Commercial Support - FibroGen Inc

Table 1: KDQoL-36 scores* by inflammation status

PO2278
Higher Frequency of Physical Activity Reduces the Risk of Kidney Function Loss in a General Non-Diabetic Population
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Background: Physical activity (PA) reduces the risk of diabetes and hypertension, known risk factors for chronic kidney disease (CKD), but there is limited data on the independent association between PA and loss of kidney function. Previous population studies of PA have reported mixed results and relied on estimated glomerular filtration rate (eGFR). All eGFR equations are biased by non-GFR related factors such as muscle mass and inflammation, making confounding likely, particularly in studies of PA. We investigated the association between self-reported PA and the annual change of measured GFR in a general population cohort.

Methods: 1627 subjects aged 50-62 years, without diabetes, cardiovascular disease or CKD were recruited from the general population in Tromso, Norway, and included in the Renal Iohexol Clearance Survey (RENIS) in 2007. Participants completed a questionnaire regarding frequency, intensity and duration of leisure-time PA, medication and comorbidities. GFR was measured using iohexol clearance at baseline and follow-up in 2013-15 and 2018-20. Linear mixed regression was used to analyze the association of PA with annual change in GFR, and logistic regression was used to assess the risk of accelerated GFR decline, defined as being those with the 10% steepest GFR decline.

Results: Mean (SD) age was 58 (3.8) years and 51% were female, median follow-up time was 11 years. Relative to participants that never exercise, the annual GFR decline rate for participants with PA once a week, 2-3 times a week or almost every day was slower by 0.40 (95% CI 0.05-0.76, p=0.026), 0.49 (95% CI 0.15-0.84, p=0.005) and

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0.52 (95% CI 0.16-0.89, p=0.005) ml/min/1.73m²/year (linear trend p=0.002), in a fully adjusted model. Increasing frequency of PA was associated with a lower odds ratio (OR) of rapid kidney function decline, with an OR of 0.25 (95% CI 0.1-0.6, p=0.004) for the highest frequency of weekly PA compared to the group that never exercise, in a model adjusted for established risk factors for GFR decline (linear trend across groups p=0.011).

Conclusions: In this population-based study with repeated measurements of GFR during 11 years of follow-up, higher frequencies of leisure-time PA are associated with slower GFR decline.

Funding: Government Support - Non-U.S.

PO2279

Serum Uric Acid Levels and Nephrosclerosis in a Population-Based Autopsy Study: The Hisayama Study

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Background: The information regarding the influence of serum uric acid levels on the pathological changes in kidneys is limited. We aimed to examine the association between serum uric acid levels and pathological findings of nephrosclerosis in population-based autopsy samples.

Methods: A total of 923 deceased subjects in a Japanese community underwent autopsy examinations between 1974 and 1994. Of these, 547 cases with available kidney tissue and health examinations data within a median of 3 years before death were eligible for the present study. Serum uric acid levels were categorized into quintiles (Q1, 1.8-3.9; Q2, 4.0-4.6; Q3, 4.7-5.4; Q4, 5.5-6.3; Q5, 6.4-12.7 mg/dl). The presence of the advanced degree of glomerular sclerosis, kidney arteriolar hyalinosis, and kidney arteriosclerosis were determined by the 90th percentile or more of a glomerular sclerosis index and an arteriolar hyalinosis index, and the 10th percentile or less of a wall-lumen ratio, respectively. A logistic regression model was used to evaluate odds ratios and their 95% confidence intervals of serum uric acid levels on the presence of all potential covariates. There was no evidence of significant associations of serum uric acid levels with arteriolar hyalinosis index and the presence of advanced arteriolar hyalinosis.

Results: Higher serum uric acid levels were associated significantly with greater age- and sex-adjusted glomerular sclerosis index and lesser wall-lumen ratio. Subjects in the Q5 groups had a significantly greater likelihood of advanced glomerular sclerosis and advanced kidney arteriosclerosis than in subjects in the Q1 group after adjusting for potential covariates. There was no evidence of significant associations of serum uric acid levels with arteriolar hyalinosis index and the presence of advanced arteriolar hyalinosis.

Conclusions: Elevated serum uric acid levels were associated significantly with advanced glomerular sclerosis and advanced kidney arteriosclerosis, but not with advanced arteriolar hyalinosis in community based autopsy samples of Japanese.

PO2280

Prescribed Medications for Nausea and Vomiting Symptoms and Incident CKD in US Veterans

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Background: Unpleasant upper gastrointestinal symptoms including nausea and vomiting prescribed medication for their treatment may have important clinical implications as prelude to incident of chronic kidney disease (CKD), a hypothesis we sought to examine in US Veterans without reduced kidney function.

Methods: In 2,524,842 US Veterans with normal baseline eGFR (≥60 ml/min/1.73m²) and available data on albuminuria in 2004-2006, we examined the association of de novo prevalent use of prescribed medications during the baseline period with incident CKD over 14 years. Associations were examined in hazard models adjusted for demographics, major comorbidities, baseline eGFR, and albuminuria category.

Results: We identified 14,813 Veterans who were incident new anti-emetic users. Patients were mean 61.6±14 years old, 7% female, 16% Black, and 5% Hispanic. Anti-emetic medication users were more likely to be female, White, smokers, with higher frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, and diabetes. Anti-emetic medication users had an almost 2-fold higher incidence rate of CKD compared to non-users (4.7% (95% CI 4.6-4.9) per 100 patient years vs. 2.4±0.048) (2.4-2.4), a faster time to incident CKD (Figure 1), and a 7% higher multivariable adjusted hazard (HR: 1.73, 95%CI: 1.69, 1.78) of incident CKD.

Conclusions: De novo prescription of anti-emetic medications in Veterans without reduced kidney function is associated with 73% higher likelihood of incident CKD independent of comorbidities and other potential confounders. Higher incident CKD likelihood may be due to prescribed anti-emetic medications or this relationship may represent the association of the unpleasant upper gastrointestinal symptoms with CKD risk, which warrants additional studies.

Funding: Veterans Affairs Support

PO2281

Polypharmacy and Potentially Inappropriate Medication Use in Patients with CKD Managed in Canadian Primary Care

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Background: Polypharmacy and the use of potentially inappropriate medications (PIMs) are an increasingly serious public health challenge attributable to aging populations and multimorbidity. This study assessed the prevalence of polypharmacy and use of PIMs in chronic kidney disease (CKD).

Methods: A cross-sectional analysis using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database (January 1, 2010 through December 31, 2018). Polypharmacy was defined as the use of ≥5 medications, excessive polypharmacy as a ≥10 medications, and PIMs as medications recommended to be avoided in CKD.

Results: The cohort was comprised of 70,331 patients (mean [SD] age, 73.1 [11.4] years; 40,502 [57.6%] female) with CKD stages G3a to G5. The most common chronic conditions were hypertension (60.8%), diabetes (29.4%), and osteoarthritis (25.4%). Overall, the prevalence of polypharmacy and excessive polypharmacy was 91.5% and 74.9%, respectively. The median number of medications was 14 (IQR 9-23). The most commonly prescribed medications were atorvastatin (29.8%), amiodipine (28.9%), and rosuvastatin (27.2%). About 45% of patients with CKD had at least one PIM, 11.1% had two PIMs, and 3.6% had three or more PIMs. The most commonly prescribed PIMs were metformin (21.7%), nitrofurantoin (16.2%), and rivaroxaban (4.5%).

Conclusions: Polypharmacy and use of PIMs are highly prevalent among patients with CKD managed in primary care. These findings highlight opportunities for interventions aimed at improving prescribing practices in the management of CKD.

Funding: Government Support - Non-U.S.

PO2282

Association of SGLT2 Inhibitors and DPP-4 Inhibitors vs. GLP-1 Agonists with Incident CKD in US Veterans

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Background: Randomized controlled trials (RCTs) have demonstrated that SGLT2 inhibitors (SGLT2i) reduce the risk of eGFR decline and ESRD as compared with placebo in patients with pre-existing CKD. These RCTs showed an initial dip in eGFR with initiation of SGLT2i that stabilized over time. Little is known about the impact SGLT2i vs. other newer anti-diabetic medications (DPP-4 inhibitors [DPP4i], GLP1 agonists [GLP1a]) upon risk of developing de novo kidney dysfunction in patients without underlying CKD.

Methods: Among US Veterans with diabetes and absence of pre-existing CKD (normal eGFR and no proteinuria) followed over 2004-18, we identified incident (new) users of SGLT2i vs. DPP4i vs. GLP1a therapy, excluding combined users of the examined classes. We examined associations of SGLT2i vs. DPP4i vs. GLP1a use with the risk of incident CKD (primary outcome) and ESRD (secondary outcome) using multivariable Cox models.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Among 39,065 diabetic patients without pre-existing CKD, 15%, 70%, vs. 15% were new users of SGLT2i, DPP4i, vs. GLP1ra, respectively. Compared to DPP4i use of SGLT2i and GLP1ra were each associated with higher risk of incident CKD: adjusted HRs (aHRs) (95% CI) 1.32 (1.18−1.47) and 1.20 (1.11−1.31), respectively (Figure 1A). However, use of SGLT2i and GLP1ra were not associated with higher risk of de novo ESRD: adjusted HRs (aHRs) (95% CI) 1.20 (0.15−9.32) and 0.62 (0.24−1.57), respectively (Figure 1B).

Conclusions: In a national cohort of diabetic US Veterans without pre-existing CKD, SGLT2i and GLP1ra use were each associated with higher risk of incident CKD as compared with DPP4i use. However, neither medication was associated with incident ESRD, suggesting that early decline with SGLT2i and GLP1ra use may be an acute/subacute effect that stabilizes over time.

Funding: Veterans Affairs Support

PO2283
Insulin Use and CKD Are Risk Factors for Mild Cognitive Impairment (MCI) or Dementia in Persons with Type 2 Diabetes
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Background: Both insulin use and CKD are risk factors for hypoglycemic episodes in patients with diabetes. Recurrent hypoglycemia is associated with increased risk of dementia. Hence, we examined whether insulin use and CKD are associated with increased risk of MCI/dementia.

Methods: We analyzed a national VA cohort (N = 855,133) with T2DM defined by ICD-9 codes and outpatient serum creatin from 1/2008 to 12/2010. Index date was the date of first outpatient serum creatinine measurement. Baseline comorbidities were defined by ICD-9 codes from 10/1999 to the index date. MCI/dementia were defined by ICD-10 codes. Those with baseline MCI/dementia were excluded and new onset of MCI/dementia was tracked from index date to 12/31/2020. A multivariate logistic regression model of baseline variables was used to develop propensity scores of baseline insulin use (24% were on insulin at baseline). A propensity score matched cohort (N = 288,374) was used to relate baseline insulin use and CKD stages with subsequent MCI/dementia in Cox regression models.

Results: Baseline mean age was 65 ± 11 yrs, 20% black and mean eGFR 72±24. There were 40,299 MCI/dementia events over 2,439,244 years of follow up. There was a graded increase in incidence rate of MCI/dementia by CKD stages and insulin use (Fig 1). In a Cox regression model adjusted for propensity scores and covariates, both insulin use and advanced CKD were associated with higher risk of MCI/dementia (Fig 2).

Conclusions: Both insulin use and advanced CKD are associated with higher risk of MCI/dementia in persons with T2DM.

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

PO2284
Incidence of CKD Stages 3-5 Among Patients on Lithium Therapy
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Background: The association between lithium use and chronic kidney disease (CKD) is not well understood, and the impact of comorbidities and other factors remains unknown. The aim of this study was to examine the risk of developing CKD stage 3 and above among individuals using lithium.

Methods: This was a retrospective cohort study of all patients in Iceland treated with lithium in the years 2008-2018. A control group was comprised of patients with affective disorders (ICD-10 codes F30-F39) who attended the outpatient clinics of the Landspitali-The National University Hospital Mental Health Services in 2014-2016 and had not been prescribed lithium. CKD stages 3-5 was defined according to the KDDIGO 2012 guidelines and eGFR was calculated from serum creatinine (SCr) using the CKD-EPI equation. Individuals with CKD 3-5 prior to 2008 and those with fewer than 2 SCr measurements during the study period were excluded. Risk assessment was performed using logistic regression.

Results: A total of 2682 persons had received lithium treatment, of whom 2051 (76.5%) were included in the study. Of those 221 (10.8%) developed CKD 3-5. Of the 1426 persons in the control group, 1010 (70.8%) were included, of whom 29 (2.9%) developed CKD 3-5. Lithium use was significantly associated with CKD development (OR 1.94, 95% CI 1.25−3.115) after adjusting for sex, age and comorbid diseases (Table).

Conclusions: Lithium treatment is a highly significant independent risk factor for the development of CKD in individuals with affective disorders.

Funding: Government Support - Non-U.S.

Factors associated with CKD, multivariable logistic regression.

PO2285
Effect of Serum Testosterone on Kidney Function in Men and Women from the General Population

Background: Testosterone may prevent kidney function decline, but at population level evidence is sparse in males, and even lacking in females. Therefore, we investigated the association between serum testosterone and kidney function in males and females from a large population-based cohort study.

Methods: Linear regression and linear mixed models were used to assess the associations of serum free and total testosterone with kidney function, including baseline assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcreat) or serum cystatin C (eGFRCys), and the urine albumin-to-creatinine ratio (ACR), and repeated assessments of eGFRCreat. Betas with their 95% confidence intervals (CI) were reported per 1 nmol/L increase in testosterone. Analyses were conducted for males and females separately.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Our study population comprised 9,484 participants (mean age 65.2 years). In models (n=1,622), higher free testosterone was associated with lower eGFRcrt (beta -0.63, 95% CI -1.05; -0.21), but higher eGFRcys (beta 0.56, 95% CI 0.07; 1.05), and lower ACR (beta -0.25, 95% CI -0.35; -0.16) at baseline. Higher total testosterone was associated with higher eGFRcrt at baseline and over time, but with lower eGFRcrt when additionally adjusted for sex hormone-binding globulin. In females (n=5,449), higher free testosterone was associated with lower eGFRcrt and eGFRcys at baseline (beta -1.03, 95% CI -1.36; -0.71, beta -1.07, 95% CI -1.44; -0.70) and lower eGFRcrt over time (beta -0.78, 95% CI -1.10; -0.46), but not with ACR. Similar results were obtained with total testosterone.

Conclusions: The association between serum testosterone and kidney function is sex-dependent, with a positive association in males and a negative association in females. The discrepant results with AGR at baseline may be explained by the effect of testosterone on muscle mass. Whether treatment with testosterone replacement therapy may be beneficial for kidney function in males with low serum testosterone still needs to be investigated. The association between testosterone and lower eGFR in females requires further study.

PO2286
Assessment of Circulating Inflammatory Cytokines Aids in the Prediction of Progression of CKD
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Background: Though Chronic Kidney Disease (CKD) is common, only a small proportion of patients progress towards the need for dialysis or transplantation. Understanding the factors which drive progression of CKD may facilitate better prediction of outcomes for patients and streamline patient care.

Methods: Inflammatory cytokines, IL-6, IL-10 and TNF-α were measured in patients with CKD. Clinical data, including demographic, biochemical, histological, and longitudinal assessments of renal function were collected for these patients. Differences in levels of circulating inflammatory cytokines were examined using independent samples, two-sided T tests, with α < 0.05. Linear regression models, using bootstrap resampling were explored to identify the ability of these cytokines to explain future eGFR. Cox proportional hazards models were explored to examine predictors of progression of CKD, defined as the need to commence dialysis or undergo transplantation.

Results: Levels of inflammatory cytokines were assessed in 226 patients with kidney disease. Higher levels were seen in those patients who experienced progression of CKD. 14% of the variance in eGFR at 12 month follow-up was explained by IL-6 levels at baseline (bias -0.0039, SE 0.036). TNF-α levels were predicted to explain 21% of 12 month eGFR (bias -0.005, SE 0.07). In a Cox proportional hazards model, patients with the highest quartile of IL-10 measurements were more likely to experience CKD progression towards the need for dialysis or transplantation (HR 4.99, 95% CI 1.62-15.32) (Likelihood ratio test = 45, on 13 df, p = 2x10^-10). Patients with lower levels of tubulointerstitial fibrosis (<50% on kidney biopsy) were less likely to experience CKD progression towards the need for dialysis or transplantation (HR 0.38, 95% CI 0.19; 0.73).

Conclusions: Higher levels of inflammatory cytokines in patients with CKD are predictive of eGFR decline and may be incorporated in models to help predict outcomes for CKD patients.

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

PO2287
Disturbance of Circadian Rhythm and CKD in Korean Adult Population
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Background: Disturbances in circadian rhythm are known to cause a number of health problems (psychosis, metabolic syndrome, cancer, etc.), however their contribution to kidney disease is not well understood. Therefore, this study evaluated the association with chronic kidney disease (CKD), sleep disturbance, and shift work in a Korean adult population.

Methods: A total of 32,429 participants who completed the National Health and Nutrition Examination Survey from 2010 to 2018 were assessed for their sleep patterns, shift work, and renal function. CKD was defined by eGFR 60 mL/min/1.73 m² or urinary albumin-to-creatinine ratio >30 mg/g.

Results: First, sleep disturbances were assessed according to sleep onset time and total sleep duration. We observed that the early bedtime group (starting sleep before 9pm) had a significantly higher CKD prevalence (OR 2.757, p = 0.001) compared to the regular bedtime group (9pm-2am), but inadequate sleep duration (<6hr) had minimal effect on CKD (OR 1.052, p = 0.745), which suggest that alterations in circadian rhythms due to sleep disturbance are associated with CKD development. In particular, there was a strong association between sleep disturbance and renal dysfunction in patients with comorbidities younger than 65 years of age. Next, work schedules were divided into two types; regular work (day or evening work) and shift work (fixed night shift, 24-hour shift, split-work). The shift-work group also had a higher prevalence of CKD compared to the regular work group (OR 1.32). However, in a multivariate analysis that adjusted for age, sex, BMI, smoking, drinking, diabetes, and hypertension, neither sleep disturbance nor shift work showed an independent association with the occurrence of CKD.

Conclusions: Our results suggest that impaired circadian rhythm may be associated with CKD development and that sleep disturbance can be an important therapeutic target for circadian rhythm.

PO2288
Mortality Risk and Life-Years Associated with CKD for Young and Older Adults
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Background: Younger individuals living with CKD face a lifetime at risk for complications, including an increased risk of mortality. There is limited data to inform individual patients with CKD across the lifespan how their risk for mortality compares to age-matched peers without CKD. The objective of this study is to provide age-specific contexts to the risk of mortality associated with a diagnosis of CKD.

Methods: We created a pooled study cohort using participants with CKD enrolled in the Chronic Renal Insufficiency Cohort along with participants aged 21-75 years with an eGFR >70mL/min/1.73m² included in the 2002-2008 NHANES surveys. Age-stratified mortality rates, along with unadjusted and adjusted hazard ratios (HR) for mortality were generated to compare differences between those with and without CKD. Mean life-years-lost (LYL) relating to CKD were calculated using CDC life tables.

Results: A total of 17,550 participants (3,746 with CKD) were included. The adjusted HR for mortality relating to CKD was highest in the 21-35yr strata (HR [95% CI]: 3.5 [3.5, 9.0]) and lowest in the 65-75yr strata (HR [95% CI]: 1.9 [1.6, 2.1]). Mean LYL secondary to CKD was inversely related with increasing age (Fig. 1). An individual aged 21yrs old with CKD could expect a mean of 15.6 LYL compared to age-matched peers without CKD. A similar comparison in a 70-yr-old would translate to 2.9 LYL.

Conclusions: Compared to age-matched peers without CKD, the risk for mortality and LYL associated with a diagnosis of CKD is highest in younger individuals. Further research is needed to elucidate the societal and personal costs of premature mortality in young adults with CKD.

Funding: NIDDK Support
Quantile Regressions for eGFR and Myocardial Fibrosis Biomarkers

PO2290

Renal Biopsy Is Mandatory in Normal Urinary Findings with Unknown Origin Hypertension or CKD

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Background: One of the most common causes of end-stage renal disease are diabetes mellitus, hypertension and chronic glomerulonephritis, however most centers do not try to find the origin of hypertension especially in chronic kidney disease patients. Most chronic glomerulonephritis patients usually associated with hematuria and or proteinuria. Most kidney centers do not recommend renal biopsy if proteinuria is absent even though associated with persistent hematuria. In order to clarify the causes of hypertension or chronic kidney diseases, our center performed renal biopsy who showed unknown origin chronic kidney disease or unknown origin hypertension even though urinary findings showed no abnormalities.

Methods: From 2014 to 2020, we performed 1,300 cases of renal biopsy, of which 272 cases showed no urinary abnormalities when performing renal biopsy. We performed renal biopsy not only in unknown origin hematuria and unknown origin proteinuria but also we performed renal biopsy in unknown origin CKD and unknown origin hypertension even though urinary findings were normal at that time of renal biopsy.

Results: Of the 1,300 renal biopsy patients, 272 (20.9%) showed normal urinary findings at that time of renal biopsy. Minor changes were detected in 2 cases among 272 cases. Most cases were serious chronic glomerulonephritis. Biopsy results were as follows: IgA nephrophy 98 cases(36%), Mild focal nonspecific glomerulonephritis 43 cases(15.8%), Focal segmental glomerulosclerosis 39 cases(14.3%), Diffuse mesangial proliferative glomerulonephritis 39 cases(14.3%), Podocyte disease 8 cases(2.9%), Membranous nephrophy 6 cases (2.2%), C1q nephropathy 5 cases(1.8%), Lupus nephritis 4 cases(1.5%), malignant hypertension 3 cases(1.1%), obesity related glomerulopathy 2 cases(0.7%), Minor change 2 cases(0.7%), C1qN 1 case(0.3%).

Conclusions: Most patients with CKD /hypertension patients without urinary abnormalities showed serious chronic glomerulonephritis such as IgA nephropyathy, FSGS, diffuse mesangial proliferative glomerulonephritis etc. kidney biopsy is mandatory in unknown origin CKD hypertension to clarify the original causes before considering antihypertensive medicine.

PO2291

Association Between Diabetes and Major Bleeding Complications of Renal Biopsy: Analysis of 76,304 Patients Using a National Inpatient Database in Japan


Background: Nephrologists have recently recognized the heterogeneity of kidney diseases in patients with diabetes and actively performed percutaneous renal biopsies (PRBs). However, the association between diabetes and major bleeding complications of PRBs remains unclear.

Methods: In this retrospective observational study using the Japanese nationwide Diagnosis Procedure Combination inpatient database, we identified patients who underwent an elective PRB between July 2010 and March 2018. The primary outcome was the occurrence of major bleeding complications defined as (i) red blood cell transfusion within 7 days after the PRB or (ii) invasive hemostasis after the PRB. Multiple regression analysis was performed to analyze the association between diabetes and major bleeding complications with adjustment for patient and hospital characteristics.

Results: We identified 76,304 patients, including 8,245 patients with diabetes. The proportion of biopsies for patients with diabetes to total biopsies increased year by year (Figure 1). Major bleeding complications occurred in 678 (0.9%) patients, including 622 (0.8%) red blood cell transfusion and 109 (0.1%) invasive hemostasis. Diabetes was significantly associated with major bleeding complications (RR, 2.66; 95% CI, 2.12-3.34).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO2292

Application of the Renal Chronicity Score on Native Kidney Biopsies: Results from the FCGG Biopsy Registry

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Background: Chronic changes on kidney biopsy strongly predict renal outcome and have important treatment implications. Sethi et al. recently proposed the renal chronicity score (RCS), a standardized pathology scoring system which uniformly scores chronic changes on kidney biopsies. We report the RCS of the biopsies included in the FCGG registry in 2018 and 2019.

Methods: The RCS is derived from the sum of the degree of glomerulosclerosis, tubular atrophy, interstitial fibrosis and arteriosclerosis, and ranges from 0 (no/minimal chronic changes) to 10 (severe chronic changes). The FCGG registry is a population-based native kidney biopsy registry in Flanders (Northern part of Belgium) that covers a population of approximately 6.5 million inhabitants.

Results: In 2018 and 2019, the RCS was reported in 1106 of 1403 adult biopsies (78,83%), with a median value of 4 (mild chronic changes, Fig. 1A). Minimal change disease (MCD) and lupus nephritis (LN) showed mostly minimal to mild signs of disease chronicity (Fig. 1B). Membranous nephropathy (MN), tubulointerstitial nephritis (TIN), ANCA-associated vasculitis (AAV) and IgA-nephropathy (IgAN) showed an increasing proportion of moderate to severe chronic changes (26%, 35%, 37%, 45%, respectively, Fig. 1B). Finally, in focal segmental glomerulosclerosis (FSGS), nephrosclerosis and diabetic kidney disease (DKD) the proportion of biopsies with moderate to severe chronic changes exceeded 50% (60%, 79%, 80%, respectively, Fig. 1B). The RCS was also higher in biopsies from older patients (Fig. 1C), although this observation is likely confounded by the etiology of kidney disease in the older age categories (i.e., more nephrosclerosis in older patients).

Conclusions: We report on the first large population-based kidney biopsy registry that systematically scores chronic changes on kidney biopsy in a standardized manner, using the RCS. Future research should validate this score by assessing the correlation with prognosis and treatment outcome in individual kidney diseases and determine whether disease-specific modifications in the chronicity classification should be made.

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PO2294

Behavioral Characteristics and Related Factors Among CKD Patients in South Korea During the COVID-19 Pandemic

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Background: The recent novel coronavirus disease (COVID-19) pandemic has led to unprecedented changes in behavior. We evaluated the current status of precautionary behavior and physical activity in chronic kidney disease (CKD) patients during the COVID-19 pandemic.

Methods: A population of CKD patients (n=306) registered in a SKETCH (Study on Kidney disease and Environment) Chemicals, Clinical Trial No. MCT04679196b) cohort recruited from June 2020 to October 2020 was included in the study. We conducted a questionnaire survey related to (1) risk perception of COVID-19, (2) hygienic behavior, (3) social distancing, and (4) physical activity during the past year (before the pandemic) and during the pandemic. To compare behaviors before and during the COVID-19 pandemic, the Wilcoxon-signed rank test was used. Logistic regression analysis was conducted to identify the relative factors related to risk perception or behavior changes.

Results: There were 187 (61.1%) patients with eGFR <45 mL/min/1.73 m². This population showed a higher degree of risk perception for COVID-19 than the general population. During the pandemic, social distancing and hygiene-related behavior was significantly increased (P<0.001). The frequency of exercise was decreased only among those with regular exercise, without diabetes, or with a lower Charlson comorbidity index (CCI) (P<0.001), with no change among the other groups. Socioeconomic status and comorbidities significantly affected behavioral characteristics regardless of the category. Age was the most significant determinant of risk perception among CKD patients. Education and income were significantly associated with precautionary behaviors such as staying at home and hand sanitizer use. Also, patients with higher CCI status significantly increased their frequency of exercise (adjusted OR 1.90, 95% CI 1.01-4.38).

Conclusions: CKD patients showed higher risk perception with active precautionary behavioral changes than the general population. Healthcare providers should be aware of the characteristics to comprise precautionary behavior without reducing the physical activity.

PO2295


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Background: Prevalence of chronic kidney disease (CKD), a pandemic condition, is generally estimated at 5-10% of the general population and increases with ageing. With the emergence of artificial intelligence, machine learning approaches could identify patients with such condition, improve our understanding of health, and provide opportunities for intervention. The aim was to automatically identify people with CKD and estimate more precisely its prevalence, which remains a real challenge.

Methods: Two sources of data were used, LPD (Longitudinal Patients Data) and LRx (Lifeflink Treatments Dynamics), including data of near 2.5 and 40 million subjects, respectively. LPD, a medical database, included 191,905 patients receiving medications usually as defined for CKD from July 1st, 2019 to June 30, 2020. Of these subjects, 1.9% had a firm diagnosis of CKD, dialysis, or kidney transplant status. These patients were followed by 1,210 general practitioners who participated in a permanent longitudinal observatory of ambulatory medicine prescriptions (LPD). LRx contained all anonymized medication dispensing in outpatient care database from a representative panel of 45% of all French metropolitan retail pharmacies. A machine learning algorithm using a gradient boosting model was trained from CKD patients identified in LPD (metrics performance - sensitivity: 68%, specificity: 99%, positive predictive value: 52%, negative predictive value: 99%, F1 score: 59%). The model was implemented in LRx to obtain the overall number of CKD patients in the period of interest. As we will underestimate the true number of CKD patients, rules-based algorithm focused on erythropoietin delivery for renal condition and keto-analog was applied on LRx. We calculated the raw number of CKD patients and extrapolated it and described demographic characteristics from November 1st 2019 to October 31st 2020.

Results: In LRx, we numbered 269,183 CKD patients corresponding to an extrapolated number of 678,102 patients with 40.8% of women and the mean age was of 77.0 years (±11.1) in the period of interest. This corresponded to a prevalence of 1.7%.

Conclusions: A combined approach using machine learning and rules-based algorithm may be useful in identifying CKD patients who require careful management of their renal condition.

Funding: Private Foundation Support

PO2297

CKD Among Patients with Dengue: A Comorbidity That Increases Hospitalization and Mortality

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Background: Dengue virus is one of the most important neglected tropical diseases in the world, with varying manifestations, including kidney involvement. The aim of this study was to investigate chronic kidney disease (CKD) and its association with outcomes among patients with dengue.

Methods: A cross-sectional study was conducted in Ceará State, northeast Brazil, in the period from January 2015 to December 2017, including all confirmed cases of dengue through clinical, epidemiology and laboratory tests (IgM specific antibodies or RT-PCR). We have made a comparison between patients with and without CKD, defined according to the KDIGO guidelines.

Results: A total of 161,880 patients were included. Patients with CKD were older (41±22 vs. 35±21 years, p<0.001), predominantly female (62 vs. 57%, p=0.004) and presented higher frequency of majority of symptoms and signs (fever: 89 vs. 86%, p=0.01; myalgia: 76 vs. 67%, p<0.001; rash: 35 vs. 22%, p=0.001; nausea: 42 vs. 23%, p<0.001). The most common comorbidities were hypertension and diabetes, which are also the most common causes of CKD (51 vs. 3.3% vs. 42 vs. 1.3%, p<0.001). Independent factors associated with CKD were: hemodialysis (OR 8.08), auto-immune disease (OR 7.73), lupus (OR 6.07), diabetes (OR 5.06), obesity (OR 4.09), hypertension (OR 3.80), and kidney stones (OR 3.03). Need of hospitalization was significantly more frequent among those with regular exercise, without diabetes, or with a lower Charlson comorbidity index (CCI) (P<0.001), with no change among the other groups. Socioeconomic status and comorbidities significantly affected behavioral characteristics regardless of the category. Age was the most significant determinant of risk perception among CKD patients. Socioeconomic status and comorbidities were significantly associated with precautionary behaviors such as staying at home and hand sanitizer use. Also, patients with higher CCI status significantly increased their frequency of exercise (adjusted OR 1.90, 95% CI 1.01-4.38).

Conclusions: CKD patients showed higher risk perception with active precautionary behavioral changes than the general population. Healthcare providers should be aware of the characteristics to comprise precautionary behavior without reducing the physical activity.
Although Provider Awareness Is High, More Than Half of US Veterans with CKD: Being Treated for Hypertension (HTN) Are Not Meeting Blood Pressure (BP) Targets

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Background: HTN is a leading cause of kidney failure in the U.S. In people with CKD, BP control is critical to slow progression to kidney failure. We sought to assess HTN awareness among providers and BP control among Veterans with HTN and CKD.

Methods: We estimated both provider awareness (ICD code for HTN) and BP control (s130/80 mmHg, ACC 2017) among ~12 million US Veterans between 2006 and 2018, aged 18+, with CKD and HTN, with 1+ outpatient visit each year. Veterans were determined to have CKD if they had either 1) an ICD diagnosis code, 2) eGFR < 60 ml/min/1.73m², and/or 3) urinary albumin-to-creatinine ratio 30+ mg/g; HTN if they had 1) a diagnosis, 2) were taking BP lowering medications, and/or 3) BP > 130/80. Treatment was defined as a prescription for BP lowering medication.

Results: From 2006 to 2018, ~94% of US veterans with CKD and HTN had a health provider-documented diagnosis code of HTN. The percentage of veterans with diagnosed HTN who were on BP-lowering medications, but did not have their BP under control (BP > 130/80 mmHg) declined from 57.6% to 51.3%. The percentage who had their BP under control increased from 30.2% in 2006 to 32.5% in 2010 but declined to 25.2% in 2018. The percentage with diagnosed HTN who were not receiving BP-lowering medications rose from 5.9% to 17.4%. The percentage of veterans with CKD and high BP who did not have a diagnosis of HTN remained between 5% and 6% throughout.

Conclusions: Provider awareness of HTN in the setting of an integrated health care system is high, as indicated by patients' recorded diagnosis of HTN. However, despite this high level of provider awareness, more than 50% of patients with diagnosed HTN in 2018 were not achieving the BP target of s130/80 mmHg, reflecting the difficulty in controlling BP in CKD patients. A better understanding of underlying factors, along with designing and implementing quality improvement programs may help improve this practice gap.

Funding: Other U.S. Government Support

PO2299

Arterial Stiffness Is Associated with the Progression of Abdominal Aortic Calcification in CKD: From the KNOW-CKD Study

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Background: Cardiovascular disease is an important cause of death in patients with chronic kidney disease. Vascular calcification is a hallmark of chronic kidney disease and an important risk factor for cardiovascular morbidity and mortality. Therefore, it is important to identify the factors that exacerbate vascular calcification for the prevention of cardiovascular complications in patients with chronic kidney disease. Although the relationship between arterial stiffness and vascular calcification is well-known, the association between the preexisting arterial stiffness and the progression of vascular calcification is not known. In this study, we analyzed the relationship between arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV) and the progression of abdominal aortic calcification (AAC) evaluated by abdominal aortic calcium score (AAC).

Methods: We selected patients who underwent lumbar X-ray and AAC measurements at the start of the study and 4 years later from the KNOW-CKD cohort. After excluding 26 patients with previous peripheral vascular disease, we analyzed 906 patients. Participants were divided into 3 groups according to their baPWV.

The progression of abdominal aortic calcification was defined as an increase in AACs after 4 years compared to the baseline.

Results: After 4 years, a total of 312 patients (34.4%) developed the progression of AAC. The progression of AAC was more frequent in higher baPWV. The incidence rates of AAC progression were 17.6%, 33.0% and 52.5% for T1 through T3 of baPWV (P<0.001). In multivariate logistic regression analysis adjusted for various cardiovascular risk factors, the odds ratio for the progression of AAC compared to T1 were 1.54 (95%CI 1.02-2.34) and 2.16 (95%CI 1.34-3.46) for T2 and T3 of baPWV.

Conclusions: Arterial stiffness is a risk factor for the progression of AAC in chronic kidney disease. This suggests that interventions that can improve arterial stiffness might be helpful in reducing cardiovascular complications in patients with chronic kidney disease.

Table: Multivariate-adjusted ORs (95% CI) for AAC progression according to baPWV

Funding: Other U.S. Government Support

POZ2300

Provider Practice Evaluation Survey: Assessment of Primary Care Provider Perspectives on Care Delivery for CKD Patients in Alberta


Background: Chronic kidney disease (CKD) is highly prevalent in the adult population of Canada, with a steady rise in end-stage renal disease. The objective of this study was to assess current modes of practice regarding CKD patients, and assess barrier and facilitators in primary care for managing and referring CKD patients using electronic consultation (eReferral).

Methods: The Provider Practice Evaluation Survey was launched for primary care providers [PCPs (family physicians or general practitioners)] licensed to practice in Alberta. Associations between barriers and facilitators to electronic consultations and clinic practice parameters; and associations between screening for CKD in patients and clinic practice parameters were analyzed. Modified Poisson regression with robust error variance was used to estimate the relative risk (RR) and 95% confidence interval.

Results: A total of 48 PCPs responded to the survey. Awareness about the availability of the eReferral tool was more likely to be a barrier to use eReferral for PCPs of South Zone as compared to PCPs from Edmonton (RR: 2.00, 95% CI: 1.07-3.74). Compared to PCPs with >5% CKD patients in their clinical practice, PCPs with 16% to 26% CKD patients were more likely to perceive barriers to use eReferral, including the ease of use for the eReferral tool (RR: 1.62, 95% CI: 1.05-2.51), and limited staff and technical support as a barrier for eReferral (RR: 2.00, 95% CI: 1.18-3.40). There was a negative association between PCPs aged between 40 and 60 years and time constraints as a barrier for eReferral (RR: 2.00, 95% CI: 1.18-3.40). There was a negative association between PCPs with >5% CKD patients in their clinical practice and referring CKD patients using electronic consultation (eReferral).

Conclusions: The results will help implement innovative steps to rectify barriers to adoption of the eReferral system and standardized CKD diagnostic guidelines to improve patient care in Canada.
PO2301

Shrunken Pore Syndrome Is Associated with a Rise in Mortality in a Community-Based Population of Middle-Aged Individuals

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Background: Chronic kidney disease (CKD) is a risk factor for increased mortality mainly due to cardiovascular disease (CVD). Glomerular filtration rate (GFR) is the best way to estimate kidney function, but it cannot be measured. Creatinine and cystatin C are two molecules that are used in clinical practice to estimate GFR (eGFR). The lower eGFR, the higher is the mortality. CKD staging is therefore a good marker of mortality and development of CVD. However, there are patients who have the same CKD stage and risk factors for development of CVD but different outcome in mortality. Shrunken pore syndrome (SPS) has shown to be a marker of increased mortality in different patient groups regardless of their measured GFR. The theory behind SPS is supposed to be a difference in the renal filtration of small molecules like creatinine compared to middle sized molecules like cystatin C. Little is known about the prevalence of SPS and the effect on mortality in the general population. The aim of our study is to investigate this.

Methods: The study population consisted of 5061 individuals from the Malmö Diet and Cancer Cardiovascular cohort community-based study that was gathered during 1991 and 2009 and followed up to January 2018. The individuals were 44–64 years old. Blood samples, anthropometric measurement and a questionnaire about lifestyle etc was available. CAPA formula was used for eGFR based on cystatin C and LMR formula was used for eGFR based on creatinine. SPS was defined as eGFRCYS ≥ 70% of eGFRcYS. Generalized propensity score was used to match individuals with SPS and those without. Kaplan-Meier estimates were used to present survival probabilities in four eGFR/eGFRCYS ratio intervals. To account for within quartet correlation, or frailty, Cox proportional hazard models with shared frailty were applied. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

Results: 405 individuals (8%) fulfilled the criterion for SPS. Median (2.5-97.5 percentiles) eGFRCYS was 63 (38-97) and median eGFRcYS was 70 (49-92) mL/min/1.73m². HR for mortality in individuals with SPS in the matched data was 2.43 (1.15 - 5.14).

Conclusion: Shrunken pore syndrome (SPS) has shown to be associated with a rise in mortality in our community-based population. Further studies are needed to explore the mechanisms behind the association between SPS and mortality.

PO2302

Associations Between Serum Biomarkers of Iron Stores and the Progression to Kidney Failure in Patients with Moderate-to-Severe CKD

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Background: We recently reported that lower levels of biomarkers of iron stores are associated with a higher risk of all-cause mortality and major adverse cardiovascular events in patients with moderate to severe chronic kidney disease (CKD). However, the impact of these parameters on the risk of kidney failure (KF), potentially a competing risk, has not been previously explored.

Methods: Patients from Brazil, France, Germany, and the US in CKDopps (eGFR <60 mL/min at enrollment, under nephrology care) and available TSAT and ferritin levels were included in the analyses. Cox models were used to estimate hazard ratios (HR) for the outcome of KF (defined as a composite endpoint including dialysis initiation, transplant, 40% decline of eGFR or from baseline, or sustained eGFR <15 mL/min/1.73m²). Over median follow-up time of 2.0 [0.6-3.0] years, there were 1800 (33%) KF events (15.7/100 pt-years).

Results: TSAT had a U-shaped association with KF (with highest HR at TSAT<15%) in the crude analysis (Model 1 of Table 1). Neither TSAT nor ferritin had a directional association with KF after adjustment for confounders (Model 2).

Conclusions: Levels of biomarkers of iron stores, as captured by TSAT and/or ferritin, are not associated with development of KF in patients with moderate to severe CKD under nephrology care. These findings further the understanding of our previous finding of a higher risk of mortality and cardiovascular events in this population with iron deficiency and high risk of CKD progression.

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PO2303

Association Between the Triglyceride-Glucose (TYG) Index and Coronary Artery Calcification Progression in Non-Diabetic CKD

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Background: Patients with chronic kidney disease (CKD), the likelihood of complications of cardiovascular disease(CVD) may increase compared to general population. Quantity of coronary artery calcification (CAC) is an important risk factor for patients with CKD without complications with atherosclerotic plaque burden and increased quantity of CAC indicates a substantially increased cardiovascular events. In previous studies, the TYG index has been reported to be associated with coronary artery calcification aggravation. We investigated whether the TYG index was related to coronary artery calcification aggravation in patients with mild renal insufficiency.

Methods: This retrospective longitudinal study included adult participants who voluntarily underwent at least two cardiac CT examination at the single center, between January 2006 and October 2018(n=1,516). The TYG index was determined using ln (fasting triglycerides [mg/dL] X fasting glucose [mg/dL]/2). Mean arterial pressure (MAP) was calculated as DBP + (SBP – DBP)/3. Mild renal insufficiency was defined as 60 ≤ eGFR ≤ 90 mL/min/1.73m² by the Chronic Kidney Disease Epidemiology Collaboration equation (mild-CKD group). CAC aggravation was defined as an increased coronary artery calcification score (CACS) in the in the follow-up period. To calculate the odds ratio for incident CKD, logistic regression analyses were performed.

Results: 1,516 patients were enrolled, of which 746 were in the mild-CKD group without diabetes. The CACS aggravation was significantly higher in participants with a tyG index of 8.9 or higher [OR 1.705 (1.351-2.152), P-value <0.001]. After adjusting for age, sex, MAP, Hemoglobin, Ca X P, potassium associated with increased risk of CAC in participants with mild renal insufficiency [OR 1.534 (1.085-2.224), P=0.027].

Conclusions: Among mild renal insufficiency without diabetes, TyG index of 8.9 or higher had a positive correlation with CAC aggravation.

PO2304

Plasma Proenkephalin and Incident CKD in REGARDS

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Background: Plasma proenkephalin (PENK) is a precursor of active enkephalins. High plasma concentrations have been previously associated with eGFR decline. Whether PENK concentrations vary by race and whether the association of PENK with incident CKD differs by race is uncertain.

Methods: In a nested cohort of 3,986 community-living participants within the REGARDS cohort, we measured PENK by ELISA. Primary outcomes were incident CKD (new eGFR < 60 mL/min/1.73m² plus 40% decline), significant eGFR decline (30% decline) and incident albuminuria (new UACR > 30mg/g) at a follow-up visit 9.4 years.
years (mean) after baseline. We used logistic regression with inverse probability sampling weights for analysis, evaluating PENK per 2-fold higher level. We tested race interactions, and explored analyses stratified by race.

**Results:** Mean age was 63 years, 48% were black, and 51% were female. Baseline eGFR was 88 ml/min/1.73m². Higher PENK was associated with all 3 outcomes in unadjusted models. In the fully adjusted models, higher PENK remained associated with significant eGFR decline and incident albuminuria. Associations differed by race. P for interaction between PENK and race was <0.01. Higher PENK was more strongly associated with incident CKD and eGFR decline and incident albuminuria in Blacks.

**Conclusions:** In community-living individuals, higher PENK is associated with significant eGFR decline and incident albuminuria, independent of eGFR, albuminuria and CKD risk factors. These associations differed by race. Future studies should determine if PENK has utility to improve eGFR risk estimation without requiring race-specific adjustments in estimates.

**Funding:** Veterans Affairs Support

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**PO2305**

Novel Approach to the Relation of Environmental Exposure and Kidney Dysfunction: Data Analysis from Korean National Environmental Health Survey (KoNEHS), 2015-2017

**Key Words:** Environment, Kidney Function, Environmental Exposure, Risk Factors, Data Analysis.

**Background:** It is well-established that guideline-concordant referrals to nephrology and included in the analysis. The mean ± SD of age was 48.2 ± 16.4. In phase 2, confirmed cases were 192 (22%) [stage-1, 14.0%; stage-2, 2.1%; stage-3, 5.5%; stage-4, 6.6%; stage-5, 11.1%]. In the multivariate logistic regression analysis, associated factors for prevalent CKD included aged ≥60 years [adjusted odds ratio (aOR), 3.02; 95% confidence interval [95% CI], 1.83 to 5.31], hypertension [aOR, 3.08; 95% CI, 2.07 to 4.59], diabetes [aOR, 2.52; 95% CI, 1.60 to 3.96], anemia [aOR, 2.59; 95% CI, 1.63 to 3.84] and presence of RCC in urine [aOR, 3.29; 95% CI, 1.71 to 5.98].

**Conclusions:** In rural and peri-urban Bangladesh, this is the first study of CKD prevalence, and repeated confirmatory testing revealed a prevalence of approximately 22%, which is higher than in urban setting. Findings suggested that CKD monitoring systems are required to assess the overall burden and effective steps should be taken to mitigate these major risk factors.

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**PO2307**

Association of XOR Activity and NLRP3 Inflammome Among CKD Patients

**Key Words:** XOR, NLRP3, Inflammome, CKD, Type 2 Diabetes.

**Background:** Previous studies have shown few result on the relationship between XOR activity and NLRP3 inflammation in non-renal patients. Methods: XOR activity was measured in non-hemodialysis patients. XOR activity was detected by fluorescence colorimetry, XO activity was detected by double binding method. After correlation analysis, multiple (stepwise) regression analysis was performed to explore the correlation between XOR and NLRP3 inflammation and the relationship with clinical data of patients.

**Results:** The correlation analysis of XOR activity, XO activity, XOR/XO ratio and NLRP3 Inflammome with biochemical indicators showed that XOR activity was significantly correlated with eGFR, DPP4, FBG, and DBP and negatively correlated with sex; Multiple linear (stepwise) regression results showed that eGFR, FBG and DBP were independent influencing factors of XOR/XO ratio; FBG and total cholesterol were independent influencing factors of Log(XO); Serum creatinine, serum sodium concentration and XOR activity were independent influencing factors of NLRP3 Inflammome, and there was no collinearity in statistical analysis. According to the value of eGFR, the patients were divided into two groups. The XOR activity, Log(XO), XOR/XO ratio, serum creatinine, area under the curve (AUC) were measured in the two groups, and the differences were statistically significant.

**Conclusions:** In CKD patients, elevated fasting blood glucose and diastolic blood pressure are independent risk factors for XOR activity, while elevated XOR activity is an independent risk factor for NLRP3 Inflammome. Therefore, controlling FBG and DBP in CKD patients has certain clinical reference significance for reducing XOR activity and further reducing NLRP3 Inflammome.

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**PO2308**

Trends in Volume, Appropriateness, and Outcomes of Referrals to Nephrology over the Last Two Decades: A Retrospective Analysis Using the Alberta Kidney Disease Network Database

**Key Words:** Nephrology, Referral, Appropriateness, Outcomes.

**Background:** It is well-established that guideline-concordant referrals to nephrology are associated with improved patient outcomes. However, some referrals are unnecessary (guideline-discordant) leading to high volumes and delays for referrals that are guideline concordant. We investigated the trends in the number of referrals to nephrology, and related outcomes in Alberta.

**Methods:** Retrospective cohort analysis of patients with at least one visit to a nephrologist from primary care between 2006 and 2019. A referral was considered appropriate based on the KDIGO defined criteria (estimated glomerular filtration rate
(eGFR) < 30 mL/min per 1.73m², albumin creatinine ratio (ACR) ≥ 30 mg/mmol or protein creatinine ratio ≥ 50 mg/mmol, or urine dipstick ≥ 2+ protein on two consecutive measurements, and/or eGFR persistently declined ≥ 5 mL/min per 1.73m² from the first eGFR measurement).

Results: Of 69,372 patients (mean age 62.5; 50.7% female), only 28,518 (41.1%) referrals met criteria as guideline-concordant (Figure 1A). Patients referred in a guideline-concordant manner were significantly more likely to be older, men, and with comorbid conditions (diabetes, hypertension, and cardiovascular disease). There has been an increasing trend in the number of guideline concordant and discordant referrals from 2006 to 2019 (Figure 1B). Patients who met guideline-criteria for referrals were likely to be prescribed renoprotective medications but more likely to experience clinical outcomes of kidney failure, cardiovascular events, and all-cause mortality.

Conclusions: The number of referrals to nephrology from primary care continues to increase, and a large proportion of these referrals were guideline discordant. Interventions targeted to primary care at reducing the number of non-guideline concordant referrals are needed.

PO2309
Microscopic Hematuria and Leukocyturia Are Highly Prevalent in East Africa and Associated with CKD
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Background: Microscopic hematuria and leukocyturia may reflect parenchymal kidney disease; there have been few population-based studies of these urinary abnormalities in Africa.

Methods: We included a population-based sample of 3,686 East Africans. We defined hematuria and leukocyturia as heme and leukocyte esterase dipstick positive (≥1+), respectively. We used sampling weights to estimate the community-based prevalence of hematuria and leukocyturia, and used weighted multivariable log-link Poisson models to assess the association of potential risk factors with these abnormalities, and separately, the association of urine abnormalities with CKD (eGFR < 60 mL/min/1.73m² or dipstick proteinuria ≥ 1+).

Results: Most participants with leukocyturia did not have hematuria or proteinuria; there was minimal overlap between hematuria and proteinuria (Figure). With sample weighting, the mean age was 38 years; 52% were female. The prevalence of hematuria was 3.7% in eastern Uganda, 2.8% in southwestern Uganda and 2.8% in Kenya. The prevalence of leukocyturia was 11.2% in eastern Uganda, 8.7% in southwestern Uganda and 2.8% in Kenya. The number of referrals to nephrology from primary care continues to increase, and a large proportion of these referrals were guideline discordant. Interventions targeted to primary care at reducing the number of non-guideline concordant referrals are needed.

Conclusions: Hematuria and leukocyturia are common in rural East Africa, with considerable regional difference. These urinary abnormalities may represent a unique pattern of kidney disease in this region.

Funding: NIDDK Support

PO2310
The Effect of Cardiometabolic Comorbidities on Risk of CKD Incidence: A Longitudinal Cohort Study
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Background: Chronic kidney disease (CKD) and cardiometabolic conditions are closely inter-related. We studied the risk of incident CKD among patients who had or developed type 2 diabetes (T2D), atherosclerotic cardiovascular disease (ASCVD), or heart failure (HF).

Methods: We conducted a longitudinal cohort study using the electronic medical records of Kaiser Permanente Northwest to identify 371,109 adult patients without CKD at baseline (first known eGFR ≥60mL/min/1.73m² between 2005-2017) and followed them through 2019 for incident CKD (two eGFR measurements <60 3-12 months apart). We assessed T2D, ASCVD and HF at baseline and prior to CKD incidence. We used time-dependent estimating equation (GEE) models to calculate age/sex-adjusted CKD incidence per 1,000 person-years independently for baseline T2D, HF, and ASCVD. Time-dependent Cox regression models were used to determine the effect of baseline or development of T2D, ASCVD and HF on CKD incidence adjusting for age, sex, race/ethnicity, renin angiotensin aldosterone system (RAAS) inhibitor and statin use, smoking, and blood pressure ≥140/90 mmHg.

Results: Study subjects were 49.7±14.9 years old and 56% were women. CKD incidence among patients with T2D or HF was more than double vs. patients without T2D or HF, and 55% higher among patients with vs. without ASCVD (Figure). In the time-dependent model, risk of CKD incidence was increased by more than 2-fold by HF (hazard ratio 2.12, 95% CI 2.05-2.19), 71% by T2D (1.71, 1.66-1.75), and 26% by ASCVD (1.22, 1.23-1.30).

Conclusions: Cardiometabolic conditions, particularly HF and T2D are independent risk factors of incident CKD. Treating the cardiometabolic-renal syndrome as a single clinical entity may benefit these patients.

Funding: Commercial Support - Boehringer Ingelheim

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

706
PO2311
Determining the Association Between Continuity of Primary Care and Acute Care Use Among Adults with CKD in Alberta, Canada
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Background: Acute care use is high among individuals with chronic kidney disease (CKD). It is unclear how relational continuity of primary care influences downstream acute care use. We aimed to determine if poor relational continuity of primary care is associated with higher rates of all-cause and potentially preventable acute care use among adults with CKD.

Methods: We conducted a population-based retrospective cohort study of adults with stages 3 and 4 CKD and at least three visits to a primary care provider between April 1, 2011 to March 31, 2014 in Alberta, Canada. Relational continuity was calculated using the Usual Provider Continuity index and descriptive statistics were used to summarize patient and acute care encounter characteristics. Adjusted rates (per 1,000 person-years) and incidence rate ratios for all-cause and CKD-related ambulatory care-sensitive condition (ACSC) hospitalizations and emergency department (ED) visits were estimated using negative binomial regression models.

Results: Among 86,475 individuals with CKD, 51.3%, 30.0%, and 18.7% of patients had high, moderate, and poor continuity of primary care, respectively. There were 77,988 all-cause hospitalizations, 204,615 all-cause ED visits, 6,489 (8.3% of all hospitalizations) CKD-related ACSC hospitalizations, and 5,461 (4.1% of all ED visits) CKD-related ACSC ED visits during a median follow-up of 2.3 years. Rates of all-cause hospitalization and ED use increased with poorer continuity of primary care in a stepwise fashion across CKD stages. Poor continuity of primary care was also associated with higher rates of CKD-related ACSC hospitalization and ED visits, particularly among individuals with stage 3 CKD.

Conclusions: Poor continuity of care is associated with increased acute care use and targeted strategies are needed to strengthen patient-provider relationships within primary care among those with CKD.

Funding: Other NIH Support - Canadian Institutes of Health Research (CIHR); Alberta Strategy for Patient Oriented Research SUPPORT Unit (AbSPORU)

PO2321
Submaximal Dose of Angiotensin Converting Enzyme Inhibitor and Angiotensin II Receptor Blockers Among Persons with Proteinuria
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Background: Underutilization of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) for treatment of albuminuria is a known quality of care gap. Among those treated with ACEI/ARB, submaximal doses represent an opportunity to improve CKD management.

Methods: Using the OptumLabs Data Warehouse, a longitudinal, real-world dataset with deidentified claims and electronic health record data, we identified adults with proteinuria, defined as either urine albumin/creatinine ≥30 mg/g or protein/creatinine ≥150 mg/g, who were prescribed an ACEI/ARB between 1/1/2015 and 12/31/2016. Among patients without apparent contraindication to ACEI/ARB dose escalation (blood pressure <130/80 mmHg, eGFR =15 ml/min/1.73m², or prior diagnosis of acute kidney injury or hyperkalemia), we examined the proportion taking the maximal recommended dose of their ACEI/ARB, overall and by demographic and clinical factors. We used multivariable logistic regression to assess factors associated with submaximal dosing.

Results: Of 79,413 patients with proteinuria receiving ACEI/ARB therapy, 50% (n=39,706) had no apparent contraindication to dose escalation. 34% (n=13,586) of these patients were on maximal ACEI/ARB doses. In multivariable analyses, younger age, Asian race, Hispanic ethnicity, higher serum potassium, and non-diabetes status were associated with submaximal dosing (Figure).

Conclusions: Among persons with proteinuria and no apparent contraindication for ACEI/ARB dose escalation, over half were on submaximal doses. Concerns over hyperkalemia may drive underdosing. However, greater attention toward maximizing ACEI/ARB dose as tolerated, especially among patients without diabetes, could optimize cardiovascular and kidney health.

Funding: NIDDK Support

PO2313
Genetic Variant rs671 of ALDH2 Gene Is Associated with Reduced Renal Function in Chinese Population
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Background: ALDH2 is a mitochondrial aldehyde dehydrogenase and ALDH2 rs671 genetic polymorphism was associated with hypertension and diabetes. Genome-wide association analysis of East Asians revealed ALDH2 rs671 variant associated with kidney function traits, but comprehensive epidemiological studies are lacking. We conducted this study to explore the associations between ALDH2 rs671 and kidney function traits in Chinese population.

Methods: A total of 15,856 individuals completed medical check-up in a single center were enrolled. ALDH2 gene mutation detection kit was used to genotype the rs671 polymorphism. Clinical laboratory data were collected from the records of medical check-up. Urine albumin creatinine ratio (UACR) was tested in 5,168 individuals and the data was log-transformed for further analysis. Linear and logistic regression analysis were used to estimate the association between rs671 SNP and renal function traits.

Results: The average age was 48.8±9.7 years and the individuals were mainly males (67.0%), 17.7%, 13.0% and 30.6% individuals were obese, diabetic, and hypertensive, respectively. Frequencies of GG, GA, and AA genotypes were 68.0%, 29.4% and 2.6%. Male individuals with A allele were associated with a significant increased level of creatinine (β = 1.057, 95% CI: 1.017, 1.098) and reduced estimated glomerular filtration rate (eGFR, β = -1.147, 95% CI: -1.317, -0.977), uric acid (β = -0.059, 95% CI: -0.083, -0.035), logUACR (β = -0.076, 95% CI: -0.094, -0.060). Similar associations were not observed in female individuals.

Conclusions: ALDH2 rs671 polymorphisms were associated with decreased renal function in male individuals other than the females. Further analyses were needed for further explore the direct and indirect effects of ALDH2 SNP on CKD, albuminuria, and proximal tubular injury.

Funding: Government Support - Non-U.S.
Impact of Dietary Fatty Acid on All-Cause Mortality According to Kidney Function Based on a Nationwide Population Study

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Background: Although the relationship between fatty acids and the risk of mortality has been long-lasting discussed, there is little evidence to support that the effect of saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) is still contentious. This study attempts to investigate the association between dietary fatty acids and all-cause mortality among the general population.

Methods: We used data from the 92,062 participants of US National Health and Nutrition Examination Survey 1999-2015. The intake of fatty acids was adjusted with the total energy intake and divided by the quartile, the first quartile group was regarded as the reference. We used a multivariate Cox-proportional hazard model to identify the impact of fatty acids on all-cause mortality.

Results: A total of 36,747 subjects were finally included in the study. During 97.9 ± 53.9 months, there were 922 (4.4%) and 3,544 (22.4%) death cases in eGFR <60 mL/min/1.73m² and ≥90 mL/min/1.73m² groups, respectively. Among 8 different SFA, hexadecanoic acid (adjusted hazard ratio [aHR] 1.13, 95% confidence interval [CI] 1.15-1.26 in 4th quartile [Q4]) and octadecanoic acid (aHR 1.13, 95% CI 1.15-1.25 in Q4) showed that greater intake was associated with the increased risk for all-cause mortality. In addition, most PUFA except eicosatetraenoic acid showed a beneficial effect on all-cause mortality. Among subjects with eGFR <60, the harmful effect of SFA was attenuated and the beneficial effect of PUFA remained in only octadecatrienoic acid. On the contrary, for the subjects with eGFR <90, the harmful effect of hexadecanoic acid (aHR 1.17, 95% CI 1.05-1.32 in Q4) and octadecanoic acid (aHR 1.16, 95% CI 1.04-1.30 in Q4) was exacerbated. The beneficial effect of PUFA was also prominent in this group; octadecatrienoic acid (aHR 0.80, 95% CI 0.67-0.95 in Q4), eicosapentaenoic acid (aHR 0.86, 95% CI 0.70-0.98 in Q4), docosapentaenoic acid (aHR 0.88, 95% CI 0.79-0.99 in Q4), and docosahexaenoic acid (aHR 0.85, 95% CI 0.79-0.99 in Q4).

Conclusions: The impact of dietary fatty acid on all-cause mortality was different in accordance to the kidney function. More specified and targeted counseling for restricting SFA and encouraging PUFA needs to be considered especially for subjects with lower eGFR.

Impact of Dietary Beta-Carotene on All-Cause Mortality According to Different Clinical Conditions, Including Decreased Kidney Function

Yae Kim,1 Kyung Ho,2 Jeonghwan Lee,3 Jae Yoon Park,1 Kyung Don Yoo,1 Yong Chul Kim,1 Jin hyuk Paek,1 Woo Yeong Park,1 Kyubok Jin,1 Seungyup Han,1 Dong Ki Kim,1 Kwon Wook Joo,2 Chun Soo Lim,1 Jung Pyo Lee,1 Keimyung University School of Medicine, Daegu, Republic of Korea; 2Seoul National University Hospital, Goyang, Gyeonggi-do, Republic of Korea; 3University of Utah, Salt Lake City, UT; 4SNUH Medical Center, Seongbuk-gu, Seoul, Republic of Korea; 5Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; 6Jeju National University, Jeju, Jeju, Republic of Korea.

Background: The beneficial effect of PUFA was also prominent in this group; octadecatrienoic acid (aHR 0.80, 95% CI 0.67-0.95 in Q4), eicosapentaenoic acid (aHR 0.86, 95% CI 0.70-0.98 in Q4), docosapentaenoic acid (aHR 0.88, 95% CI 0.79-0.99 in Q4), and docosahexaenoic acid (aHR 0.85, 95% CI 0.79-0.99 in Q4).

Conclusions: The impact of dietary fatty acid on all-cause mortality was different in accordance to the kidney function. More specified and targeted counseling for restricting SFA and encouraging PUFA needs to be considered especially for subjects with lower eGFR.

PO2316

Reduced Differences in Clinical Outcomes Between Black and White Veterans with Incident CKD After Removal of Race from Estimated Glomerular Filtration Rate (eGFR)

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Background: Assessing outcomes for racial subgroups can guide strategies to mitigate health and healthcare inequalities. We assessed differences in clinical outcomes in White versus Black veterans undergoing dialysis, and evaluated the effect of race out of the eGFR equation.

Methods: We evaluated the impact of race on the association between eGFR and outcomes in a cohort of US Veterans Health Administration who had incident CKD stage G3 or higher (i.e., first eGFR <60 mL/min/1.73 m² for ≥3 months) between 2007 and 2016. eGFR values were calculated first using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) with its race term included and again using the same equation without the race coefficient (CKD-EPI-RACEOut). We examined risks of initiating replacement therapy (KRT) and death in Blacks and Whites, with follow-up from incident CKD until May 31, 2018 or up to 10 years.

Results: 115,374 Black veterans had incident CKD defined by CKD-EPI-RACEOut vs. 507,303 White veterans by CKD-EPI, with mean ages at CKD incidence of 64, 67 and 73 years, respectively. Blacks with CKD defined by CKD-EPI-RACEOut had lower rates of both KRT and death (8.2 and 44.8 per 1000 patient-years, respectively) compared with Blacks by CKD-EPI (Table). After adjustment for age, sex, race, eGFR at CKD incidence, and CKD incidence year, Blacks by CKD-EPI-RACEOut had a 41% greater risk of KRT than Whites, a markedly decrease from the 172% greater risk with CKD-EPI. Also, Blacks by CKD-EPI-RACEOut had a 7% lower risk of death than Whites, in contrast to a 10% greater risk of death with CKD-EPI.

Conclusions: Compared to Whites, Blacks with incident CKD defined by CKD-EPI-RACEOut without race coefficient had a beneficial effect on all-cause mortality.

Funding: NIHDK Support

Hazard ratios of outcomes for Black versus White veterans with incident CKD

PO2317

Reducing the Removal Rate Coefficient from Estimation of Glomerular Filtration Rate (eGFR) at the University of Washington

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Background: The inclusion of the race coefficient in eGFR estimates for patients identified as Black has been widely debated. In response, our institution eliminated the race coefficient when reporting eGFR on June 1, 2020. We evaluated changes in prescription of metformin, dialysis initiation and referral to subspecialists among Black and non-Black patients before vs. after the change in eGFR reporting.

Methods: We manually reviewed data of self-identified Black patients with CKD within the UW system between June through November of 2019 (before change in eGFR reporting) and 2020 (after change in eGFR reporting). In addition, data from the electronic medical record (EMR) was extracted for subspecialty referral rates for Black and non-Black patients during this same time frame. We compared 6-month data pre/post change of eGFR and determined differences in: initiation and discontinuation of metformin, dialysis treatment and referral to subspecialists among Black and non-Black patients before vs. after the change in eGFR reporting.
PO2319

Comparing Estimated Glomerular Filtration Rates (eGFR) for US Black Veterans with and Without the Black-Race Coefficient and Normalization to a Fixed Body Surface Area (BSA)
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Background: The CKD-EPI estimation of GFR includes two corrections: 1) increasing eGFR for Blacks by 15.9% to more accurately reflect measured GFR; 2) normalizing eGFR in all races to a fixed value (1.73 m²) of BSA to compare across populations. We aimed to assess the impact of removing both corrections—separately and together—on the prevalence of CKD in Black US Veterans.

Methods: Among 7 million Black US Veterans, aged 18+ with at least one serum creatinine lab measurement (2006-2018), we estimated the prevalence of eGFR < 60, using four GFR-correction methods: 1) eGFR using the CKD-EPI equation with the Black-race coefficient and normalized to a BSA of 1.73 m²; 2) #1, without the Black-race coefficient; 3) #1, without normalization for BSA; and 4) #1, without the Black-race coefficient or normalization for BSA.

Results: Among Black Veterans, the average age was 57 years, 87% males, and average BSA was 2.11 m². The prevalence of CKD varied appreciably by the method of GFR estimation. CKD prevalence was highest (15-20%) throughout the 13-year study period without use of the Black-race coefficient (#2) and lowest (6-8%) without normalization for BSA (#3). The method with neither the Black-race multiplier nor BSA normalization (#4) yielded similar estimates of CKD prevalence as the CKD-EPI method of eGFR estimation (#1), differing by <2% throughout the study period. Patient-level agreement between the latter two methods was nearly 90%.

Conclusions: Our results show good agreement between Black Veterans classified as having CKD using the CKD-EPI equation with both corrections and those same veterans classified with CKD without either correction. Pending recommendations from the NKF-ASN Task Force, the latter method (#4) offers a simplified procedure to provide individualized GFR estimates on the original scale (mL/min) for all individuals.

Funding: Other U.S. Government Support

PO2318

Elimination of the Race Coefficient from eGFR Calculation on Clinical Care and CKD Research Among a National US Veteran Cohort
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Background: Elimination of the race coefficient from the CKD-EPI equation has been proposed as an important step to improve healthcare disparities faced by Black persons with chronic kidney disease (CKD).

Methods: We identified U.S. Veterans with incident non-dialysis CKD stages 3-4 based on laboratory data from 2005-2019 from the Veterans Affairs (VA) Corporate Data Warehouse. Demographic characteristics and laboratory values were used to calculate estimated glomerular filtration rate (eGFR) by the CKD-EPI equation with and without the race coefficient. We identified Black persons who were reclassified from non-CKD to CKD status or to a different CKD stage, as well as individuals whose race was not reported and eGFR could not be calculated using a race-based equation. The number of additional persons with CKD identified without the race coefficient was evaluated by VA station.

Results: There were 1,765,410 individuals with CKD stages 3-4 by race-based eGFR. Eliminating the race coefficient resulted in reclassification of 119,142 (35.2%) Black individuals as having CKD when eliminating the race coefficient. Median (IQR) number of reclassified individuals per VA station was 470 (110.5-1,393) reclassified Black persons and 1,550 (584-2,665.75) individuals of unidentified race (Figure).

Conclusions: Eliminating the eGFR race coefficient will lead to substantial but variable impact on clinical care and CKD research across VA locations nationally. Ideally, this shift will achieve more equitable clinical outcomes for Black persons and expand inclusion in CKD clinical trials and observational research to advance CKD care.

Funding: Veterans Affairs Support

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709
associated with higher ESRD prevalence in the West and parts of the Midwest (Fig 1b). PM2.5 was associated with higher prevalence in the East North Central and South West Central regions (Fig 1c).

Conclusions: Variation exists in the association between environmental factors, SDOH and the presence of ESRD geographically. It highlights the importance of attention to the environment and community-based SDOH, toward preventing and managing ESRD based on residence and individualized patient care.

Funding: Veterans Affairs Support

Figure 1 Distribution of prevalence of ESRD and the association between social and environmental characteristics and prevalence of ESRD at county level

(a) Distribution of prevalence of ESRD (per 1,000 person-years)

(b) Coefficient of neighborhood disadvantage index in the GWR model

(c) Coefficient of mean of daily PM2.5 in the GWR model

PO2322

Three New Race-Free, Community-Based Equations to Estimate GFR: The Machine Learning Estimation of Renal Function (MLERF) Equations

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Background: As inclusion of race in glomerular filtration rate (GFR) estimation has become an increasingly controversial issue, it is of vital importance to propose race-free equations and evaluate their performance.

Methods: Using Multivariable Fractional Polynomials (MFP), Generalized Additive Models (GAM), and Random Forests (RF), we developed three new GFR estimating equations from the community-based Genetic Epidemiology Network of Arteriopathy Study (GENOA) study (N=1010). We then compared performance of the new equations to the CKD-EPI creatinine equation using the Epidemiology of Coronary Artery Calcification (ECAC) cohort study and the Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD) (N=792). Due to lack of black participants in external data, we also evaluate performance of equations in Black participants internally using development data. A rigorous bootstrapping method, allowing equation coefficients to change for each bootstrap sample, was used to evaluate performance of our new equations to address the issue of overfitting.

Results: Our final equations were based on creatinine, age and sex. The addition of race yielded only minor nonsignificant improvements in RMSE and thus race was not included in the final equations. In external data (Figure), our new equations showed similar P30, RMSE, bias and precision compared to the CKD-EPI creatinine equation which included race as a predictor. Our equations also showed marked improvements in terms of bias and accuracy for Black participants over the CKD-EPI creatinine equation in the development data.

Conclusions: Performance of our new race-free equations using community-based cohorts were comparable to CKD-EPI creatinine equation in external validation and superior in Black participants in internal validation. Our study indicated that race can be removed from equations to estimate GFR in Black and White participants without significantly sacrificing equation performance.

PO2321

Facility-Level Variation and Racial Disparities in Albuminuria and Serum Creatinine Dual Testing in the US Veterans Health Administration (VHA) Health Care System

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Background: Simultaneous urine testing for albumin (UAlb) and serum creatinine (SCr), i.e., ‘dual testing’, is now an accepted quality measure in the management of diabetes. As kidney disease is defined by both UAlb and SCr testing, this approach could be more widely adopted in kidney care. We therefore sought to assess facility-level variation and racial differences in performance of dual testing in the integrated VHA health care system.

Methods: We included patients with any inpatient or outpatient visit to the VHA during the period 2009-2018. Dual testing was defined as UAlb and SCr testing in the outpatient setting within a fiscal year. A generalized linear mixed-effects model was applied to explore individual level (demographics and comorbidities) and facility level predictors of receiving dual testing.

Results: We analyzed data from approximately 6 million veterans per year (total n=69,102,389; 91.1% male). Dual testing increased on average from 17% to 21%, but varied substantially among VHA centers (0.3% to 43.7% in 2018) (Figure). Dual testing was strongly associated with diabetes (odds ratio [OR]: 10.4, 95% CI 10.3-10.5, p<0.0001) and not associated with VHA center complexity level. Despite a higher proportion of Black veterans receiving dual testing compared to White veterans (24.0% vs 21.7% in 2018), they were less likely to be tested after adjusting for other individual and facility characteristics (OR: 0.93, 95% CI 0.92-0.93, p<0.0001).

Conclusions: Performance of dual testing varied among VHA centers and is low in both White and Black veterans. Simultaneously incorporating UAlb and SCr for kidney care may help improve both risk stratification and management of individuals with or at risk of kidney disease.

Funding: Other U.S. Government Support

Figure 2 Variability in albuminuria and serum creatinine dual testing in the Veterans Health Administration

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PO2324

Effect of Removing Race Coefficient (RC) from Estimated Glomerular Filtration Rate (eGFR) Among Black Adults in the US Military Health System (MHS)

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Background: The use of race in calculating eGFR is under scrutiny as a possible contributor to healthcare disparities in the US. Using the MHS electronic medical record, we evaluated the effect in Black adults of removing eGFR race adjustment on the overall prevalence of chronic kidney disease (CKD) and on the prevalence at specific levels of eGFR important in clinical decision-making.

Methods: Fiscal Year (FY) 2015 data were extracted from the MHS Data Repository for individuals of Black race aged ≥18 without end-stage kidney disease. eGFR was calculated from serum creatinine using the CKD-EPI equation both with and without adjustment for Black race. CKD was defined as having the most recent eGFRs in the FY persistently <60 mL/min/1.73m2 for more than 3 months (KDIGO criteria). Statistical significance was determined by chi-square.

Results: 136,934 Black individuals (age=43±14 years, 38% female, 40% active duty) had serum creatinine measured a total of 259,930 times. With RC, mean eGFR was 98.1±25.7, 4.5% had at least one eGFR <60, and 1.3% met CKD by KDIGO criteria (Table). Removal of RC decreased mean eGFR to 84.7±22.2 (Δ=−13.5±3.6) and increased CKD prevalence to 2.1% (Δ=68%). Without RC, 0.9% of those with GFR≥60 were reclassified as having CKD stage 3 and 5.6% of those with CKD stage 3 reclassified into CKD stages 4-5. Without RC the prevalence of CKD stages 3b-5 increased by 75%, of CKD stages 4-5 by 65%, and of eGFR<20 (eligible for transplant listing) by 71%. Among active duty, removal of RC increased prevalence of CKD by 102% and of CKD stages 3b-5 by 68%.

Conclusions: Removal of the RC resulted in significant reclassification from non-CKD to CKD and from lower to higher stages of CKD. Consequences for patient education, treatment decisions, resource utilization, and clinical outcomes may benefit from future study. The views expressed in this abstract are those of the authors and do not reflect official policy of the Departments of Army/Navy/Air Force, Department of Defense, Department of Health and Human Services, or the US Government.

Funding: Other U.S. Government Support.

PO2325

Social Determinants of Health and Estimated GFR in the MDRD Study

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Background: Use of race in medical algorithms is facing increasing scrutiny. One concern is that race differences do not reflect biological differences, but rather differences in social determinants of health (SDH). The MDRD Study equation was the first eGFR equation to include race [self-identified and categorized as Black vs non-Black] in addition to age, sex and serum creatinine (Scr), due to observed differences between Black and non-Black individuals in mean measured GFR (mGFR) (1.21 times higher with the same age, sex and Scr) and mean Scr (17.1% higher for the same age, sex and mGFR, accounting for mGFR measurement error). Subsequent analysis suggested higher mean creatinine excretion and lower mean creatinine secretion in Black individuals. Here we explore the impact of SDH on the Black race coefficient in the MDRD Study equation and on the racial difference in observed Scr in the MDRD Study.

Methods: SDH and related variables included income, household size, education, employment, marital status, dietary protein and creatinine excretion. We examined the magnitude of the Black race coefficient and the observed race difference in Scr without and with adjustment for SDH variables.

Results: Among the 1628 participants at baseline visit 3, mean mGFR was 40 (range 5-168) and 12% were Black individuals. There were significant differences between Black and non-Black individuals for all SDH except dietary protein. Addition of SDH (Figure) did not substantially alter the Black race coefficient in eGFR (left) or the race difference in mean Scr (right).

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711
Impact of Race/Ethnicity on the Current Screening Approach for CKD

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Background: KDIGO recommends screening for chronic kidney disease (CKD) with both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR). Screening is advised for people with diabetes mellitus, hypertension and/or cardiovascular disease (CVD). People of African descent are at increased risk for CKD, while several reports indicate that the screening approach insufficiently capture CKD in this group. eGFR correction for African race/ethnicity may contribute to this discrepancy, but age and socioeconomic status (SES) may be involved. We assessed whether CKD detection is influenced by race/ethnicity correction and we defined how age >50 yr or lower SES influence CKD detection.

Methods: Baseline data of 21,617 participants (mean age 44 yr, 43% male) of Dutch (4,564), South-Asian Surinamese (3,043), African Surinamese (4,151), Ghanaian (2,339), Moroccan (3,614) and Turkish (3,596) ethnicity included in the multi-ethnic HELIUS cohort study (Amsterdam, The Netherlands) were analysed. We defined CKD as eGFR (CKD-EPI formula, <60mL/min/1.73m²) and/or ACR (a3mg/mmol). Detection rate was characterised by the c-statistic for three screening approaches in each ethnic group: I) the traditional approach (i.e. screening when having diabetes mellitus, hypertension and/or CVD); II) the traditional approach plus age >50yr; and III) the traditional approach plus low SES (i.e. none or elementary schooling). C-statistic with and without correction for race/ethnicity were compared.

Results: Of participants, 2335 (11%) had CKD. Estimated CKD was slightly more prevalent in participants of African Surinamese (11 vs 13%) and Ghanaian (12 vs 14%) descent, when the correction for race/ethnicity was discontinued. Compared to approach I, approach II and approach III did not have a higher c-statistic, overall and within African Surinamese and Ghanaian ethnicity. C-statistic with both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR) (KDIGO guidelines recommend eGFR and ACR screening), and estimated GFR (eGFR) using Scr (eGFRcys) using the MDRD Study or CKD-EPI equation are often used interchangeably. KDIGO guidelines recommend eGFRcys or eGFR using the MDRD Study or CKD-EPI equation as the initial test in adults, and confirmatory tests using serum cystatin C (eGFRcys or eGFRcys-cys), measured creatinine clearance (mClcr) or measured GFR (mGFR) using exogenous filtration markers. Methodological issues of CKD screening are beyond the scope of this study.

Conclusions: Our study shows that discontinuation of the race/ethnicity correction, or addition of age >50 yr and low SES as criteria for CKD screening have little impact on the detection rate of the currently advised screening approach.

Impact of Race/Ethnicity and Age on Survival in Advanced CKD

Patients Treated with Conservative Management vs. Dialysis

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Background: Given evidence that dialysis may not offer survival benefit nor improved quality of life in certain groups (elderly, multi-morbid), there is growing interest in conservative management (CM) as an alternative treatment strategy for advanced CKD. Yet little is known about the impact of CM vs. dialysis on CKD outcomes, including mortality, across different racial/ethnic and age groups.

Methods: In a national cohort of 309,188 advanced CKD patients (26 eGFRs <25 separated by ≥90 days), we compared mortality rates in patients treated with CM vs. dialysis from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-3yrs of the index eGFR (1st eGFR <25, with the former group parsed according to timing of dialysis initiation, defined as late, intermediate, vs. early dialysis (eGFRs <5, 5<10, vs. ≥10 at dialysis transition). We used Poisson regression to compare mortality rates in CM vs. dialysis patients across race/ethnicity and age.

Results: Whereas late, intermediate, and early dialysis had higher mortality rates than CM among Non-Hispanic Whites across all age groups, in Hispanic patients CM and dialysis had similar mortality rates across all ages. In Non-Hispanic Blacks, Asians, and Other races/ethnicities, CM vs. late dialysis had similar mortality rates among those ≥75 yrs old, whereas CM demonstrated survival benefit vs. all dialysis groups in younger ages.

Conclusions: In a diverse, nationally representative cohort of CKD patients, we observed differential relationships between CM vs. dialysis on mortality rates across race/ethnicity and age. Further research is needed to determine which patient characteristics and health services optimize candidacy and choice of CM vs. dialysis to enable a personalized approach.

Funding: NIDDK Support

Evaluation of the Cambridge GFR Estimating Equation in a Diverse Population

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Background: Evaluation of GFR is not standardized in oncology; serum creatinine (Scr) estimated creatinine clearance (eClcr) using the Cockcroft Gault equation, and estimated GFR (eGFR) using Scr (eGFRcys) using the MDRD Study or CKD-EPI equation are often used interchangeably. KDIGO guidelines recommend eGFRcys or eGFR using the MDRD Study or CKD-EPI equation as the initial test in adults, and confirmatory tests using serum cystatin C (eGFRcys or eGFRcys-cys), measured creatinine clearance (mClcr) or measured GFR (mGFR) using exogenous filtration markers. Methodological issues of CKD screening are beyond the scope of this study.

Results: Study populations included the CKD-EPI 2009 external validation population [n=3771, mean (SD) age 49.2 (14.6), mGFR 69.2 (35.5) ml/min/1.73 m², men 54.1%, African American 10%, diabetes 28.2%, and CKD-EPI 2012 external validation population [n=1119, mean (SD) age 49.9 (16.6) years, mGFR 68.9 (41.0) ml/min/1.73 m², men 59.3%, African American 3%, diabetes 53.1%]. (Note: study participants were not included in the development of the CKD-EPI equations.) No eGFRcys equation, including CamGFRcys, performed better than the CKD-EPI equation. As previously reported, CKD-EPI eGFRcys-cys performed better than CKD-EPI eGFRcys or eGFRcys (Williams et al. Clin Cancer Res 2021), which performed better than CKD-EPI eGFRcys (Williams et al. NEJM 2012).

Conclusions: In conclusion, eGFRcys using CamGFRcys is not more accurate than using CKD-EPI in a diverse population. Studies comparing CamGFRcys vs. CKD-EPI equations in patients with cancer are needed.
PO2329
Racial and Ethnic Predictors of Hyperkalemia Recurrence
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Background: Understanding predictors of recurrent HK may help healthcare providers provide a more individualized approach to HK management. This study aims to explore if race and ethnicity are independently associated with recurrent HK.

Methods: The cohort consisted of 2,457,498 US veterans who had a HK event (sK ≥5.0 mEq/L) between 2004 and 2018. We evaluated possible demographic predictors of 1-year HK recurrence using Fine and Gray competing risk regression model, which was the competing event was all-cause mortality within 1 year after index HK event. We defined HK recurrence as the third or later potassium measurement after the index HK measurement, and patients need to have at least one or more normal potassium measurements (≥mEq/L) between the HK events.

Results: Cohort mean age was 63±13yrs, mean index potassium level was 5.3±0.29 mEq/L, and median (IQR) index eGFR was 68 (49, 86) mL/min/1.73m²; 96% were male, 13% were Blacks, and 6% were Hispanic. Overall, 17% of patients had a HK recurrence within 1 year after index HK occurrence. Black patients had a 19% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.19 [1.18, 1.20]) compared to White patients. Hispanic patients had a 34% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.34 [1.32, 1.36]) compared to non-Hispanic patients. Other predictors for high risk of 1-year HK recurrence include older age (15% higher for each 15 year increment of age) and male (22% higher compared to female) (Table). Conclusions: Being Hispanic, Black, male, or older age, was associated with a higher risk of HK recurrence within 1 year after index HK event. Further studies are needed to understand the reasons for these disparities and their potential associations with clinical management of HK.

Funding: Commercial Support - AstraZeneca

Figure 1. Variables associated with incident HK in each ethnic group, analysed by (A) Logistic Regression (LR), (B) Gradient Boosted Machine (GBM) and (C) Random Forest (RF).

PO2330
Ethnic Differences for Incident CKD in Asians
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Background: Understanding the predictors of recurrent HK may help healthcare providers provide a more individualized approach to HK management. This study aims to explore if race and ethnicity are independently associated with recurrent HK.

Methods: The cohort consisted of 2,457,498 US veterans who had a HK event (sK ≥5.0 mEq/L) between 2004 and 2018. We evaluated possible demographic predictors of 1-year HK recurrence using Fine and Gray competing risk regression model, which was the competing event was all-cause mortality within 1 year after index HK event. We defined HK recurrence as the third or later potassium measurement after the index HK measurement, and patients need to have at least one or more normal potassium measurements (≥mEq/L) between the HK events.

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Funding: Commercial Support - AstraZeneca

Figure 1. Variables associated with incident HK in each ethnic group, analysed by (A) Logistic Regression (LR), (B) Gradient Boosted Machine (GBM) and (C) Random Forest (RF).

PO2331
Muscle Mass and Estimates of Renal Function: A Longitudinal Cohort Study
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Background: Current guidelines suggest using creatinine-based estimated glomerular filtration rate (eGFRCr) as measurement of renal function, but muscle mass as key determinant of creatinine after renal function may lead to imprecise estimates. We explored effects of 24-hour height-indexed creatinine excretion rate (CER index) – as accurate marker of muscle mass – on eGFRCr and muscle mass-independent cystatin C-based eGFR (eGFRCys) and predicted probabilities of misclassification given age, sex, and CER index.

Methods: We included 8,076 community-dwelling individuals enrolled in the PREVEND study. Missclassification was defined as eGFRCr ≥60 ml/min/1.73 m² when eGFRCys was <60 ml/min/1.73 m². Cross-sectional associations were quantified with multiple regression and logistic regression and longitudinal associations with linear mixed-effects models.

Results: In a simulated 70-year-old male with low muscle mass (CER index of 4.6 mEq/L,24 hour) predicted baseline eGFRCr and eGFRCys were 87.5 and 60.5 (difference: 27.0) ml/min/1.73 m², respectively (Figure). Percentages (95% CI) of misclassification in males and females older than 60 years with low muscle mass were 18.5% (14.8% to 22.1%) and 15.2% (11.6% to 18.8%), respectively. Over time, for that same 70-year-old male, eGFRCr and eGFRCys disagreed with 2.3, 4.9, 7.7, and 10.7 ml/min/1.73 m² at baseline, 5 years, 10 years, and 15 years of follow-up, respectively.

Conclusions: Low muscle mass may cause considerable overestimation of single measurements of eGFRCr. Muscle wasting may cause spurious overestimation of repeatedly measured eGFRCys. Implementing muscle mass-independent markers for estimating renal function, like cystatin C as superior alternative to creatinine, is crucial to accurately assess renal function in settings of low muscle mass or muscle wasting.
Muscle Is a Non-GFR Determinant of Serum Filtration Marker Levels and Is Associated with Differential Accuracy of GFR Estimating Equations in Older Adults

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Background: Current GFR estimating equations using creatinine are limited by association with muscle. It is not known whether this is true for recently developed equations using novel filtration markers. These associations are relevant for older adults in whom reduced muscle mass is common.

Methods: In a cross-sectional analysis of 540 community dwelling older adults in Reykjavik, Iceland, serum levels of creatinine (Cr), cystatin C (Cys), and novel filtration markers (beta-trace protein [BTP], beta-2-microglobulin [B2M], N-acetylthreonine, pseudouridine, phenylacetylglutamine, and tryptophan) were measured, and GFR was measured using clearance of iohexol (mGFR). GFR was estimated from Cr, Cys, or panels of novel filtration markers using CKD-EPI equations. Thigh muscle area (TMA) was assessed using computed tomography. The association of each filtration marker with TMA was determined using linear regression with adjustment for mGFR. GFR measurement error, age, and sex. The performance of the estimating equations was assessed using bias and percent of large (≥30%) errors (1-P30) among those in the lowest sex-specific quintile of TMA compared to the upper four quintiles.

Results: Mean age was 80 (SD 3.8) years, with a mean mGFR of 63 (SD 16) ml/min/1.73m². After adjusting for mGFR, all filtration markers had a residual association with TMA for eGFR from Cr and/or Cys, but differed across age classes. Above 65 years, CKD-EPI appeared to overestimate and underestimated eGFR from Cr and/or Cys but not for panel eGFR equations (see figure).

Conclusions: Panel eGFR may be preferable in older adults with low muscle mass. Practical tests are needed to identify individuals with low muscle mass for whom eGFR from Cr and Cys may be less accurate.

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PO2333

Gender-Specific Glomerular Filtration Rate Reference Values for Healthy Individuals Aged 18 to 90 Years

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Background: Normal glomerular filtration rate (GFR) values based on a reference method are lacking in the elderly. We measured GFR (mGFR) in healthy individuals 18 to 90 years of age to describe normal mGFR decline with age, by gender, and evaluated the performances of GFR-estimating equations in this population.

Methods: We measured GFR with renal clearance of 125I-EDTA in 630 healthy men and women, aged 18-90 years. GAMLSS were used to provide reference values of GFR, and a piecewise linear regression model, to assess the relationship between GFR, age and gender. Bias, precision and accuracy of the CKD-EPI and FAS equations were evaluated.

Results: Participants (43% men) had a mean mGFR of 90.5 ± 15.9 ml/min/1.73m². The 95th percentile stayed above 60 ml/min/1.73m² up to 80 years in men, but reached this threshold at age 63 in women, 25% of them getting below at age 76. In both genders, mGFR distribution physiologically declined as from 40 years (Figure), significantly faster in women than in men, 0.83 ± 0.09 vs 0.67 ± 0.07 ml/min/1.73 m² per year, p<0.001. Overall, median bias was significantly lower for the FAS than the CKD-EPI equation (-1.6 [95%CI: -2.9 ; -0.1] vs 3.4 [1.8 ; 4.9] ml/min/1.73 m², p<0.0001), whereas precision and P30 accuracy, 6.6 [4.9 ; 8.8] for FAS vs 8.5 [6.6 ; 10.9] for CKD-EPI, did not significantly differ between them. Performance metrics were similar in men and women, but differed across age classes. Above 65 years, CKD-EPI appeared to overestimate and FAS to substantially underestimate mGFR.

Conclusions: Ageing appears to be associated with faster GFR decline in women than in men, which may explain the paradoxical association of high CKD prevalence and low kidney failure incidence in women. Age- and gender-specific reference values should be considered for CKD diagnosis and drug dosing guidelines, particularly in the elderly.

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PO2334
Epidemiology of CKD Based on Age-Adapted GFR Thresholds
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Background: Age-adapted GFR criteria for definition of chronic kidney disease (CKD) have been proposed to account for normal age-related decline in kidney function. The aim of this study was to determine the prevalence and incidence of CKD stages 1-5 based on age-adapted GFR thresholds compared with current KDIGO GFR criteria.

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical data, including ICD-10 diagnosis codes, were retrieved from nationwide electronic medical records. Estimated GFR was calculated from SCr using the CKD-EPI equation. CKD was defined as presence of kidney damage, either proteinuria or ICD-10 diagnosis codes indicative of kidney disease, or reduced eGFR for ≥3 months. Reduced eGFR was defined as <60 mL/min/1.73 m² according to the standard KDIGO criteria or based on the following age-adapted thresholds: <75 mL/min/1.73 m² for age <40 years, <60 mL/min/1.73 m² for 40-65 years and <45 mL/min/1.73 m² for age ≥65 years. Incidence of CKD was calculated in individuals without evidence of CKD at study entry. Prevalence and incidence were standardized to the EU-27 population.

Results: We obtained 2,120,147 SCr values for 218,437 individuals. The median age was 46 (range, 18-107) years; 47% were men. A total of 25,996 individuals met the KDIGO criteria for CKD compared with 17,593 when the age-adapted criteria were applied. The mean annual age-standardized prevalence per 100,000 overall and for men and women was 5940, 5130 and 6750, respectively, using the KDIGO criteria, and 3640, 3270 and 4010, respectively, applying the age-adapted GFR thresholds. The mean annual age-standardized incidence of CKD per 100,000 overall and for and men and women was 671, 649 and 694, respectively, using the KDIGO criteria and 501, 480 and 522, respectively, applying the age-adapted thresholds.

Conclusions: This nationwide Icelandic study comprising SCr values and other markers of kidney damage for the majority of the Icelandic population demonstrates a markedly lower CKD prevalence and incidence with use of age-adapted GFR thresholds as compared with the standard KDIGO criteria.

Funding: Government Support - Non-U.S.

PO2335
Estimated Glomerular Filtration Rate Equations Based on Cystatin C Are Determined by Bioimpedance-Retrieved Fat Mass Index in Swedish Adults
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Background: The growing burden of obesity and its associations with chronic kidney disease (CKD) is becoming a hot topic for nephrologist. CystatinC, a marker of kidney function, tends to be increased in obesity. We hypothesize that bioimpedance acquired fat mass index acquired is associated with estimated glomerular filtration rate (eGFR) based on cystatinC.

Methods: 5061 subjects, born 1926-45, were selected from the population based on age <40 ≥65 years. Women with high FMz tended to have higher body mass index compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMIz (Fig.1). Women with high FMIz tended to have higher body mass index acquired compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMIz groups in both sexes.

Conclusions: CystatinC correlated with fat weight (kg), FMI and FMz in both sexes, meanwhile creatinine was not associated with muscle mass. Significant sex difference observed in high FMz group revealing lower CAPA and lower CKD-EPI cystatin C values in women and no differences in creatinine based eGFR both in men and women (Fig.1). Women with high FMz tended to have higher body mass index compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMIz groups in both sexes.

Results: CystatinC correlated with fat weight (kg), FMI and FMz in both sexes, meanwhile creatinine was not associated with muscle mass. Significant sex difference observed in high FMz group revealing lower CAPA and lower CKD-EPI cystatin C values in women and no differences in creatinine based eGFR both in men and women (Fig.1). Women with high FMz tended to have higher body mass index compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMIz groups in both sexes.

Conclusions: The correlation between cystatinC and fat weight may be due to several reasons. Obesity induced CKD is one. Further studies are warranted to exclude that obesity induced CKD is one. Further studies are warranted to exclude that cystatinC originates from adipose tissue. The use of cystatinC eGFR equations should be used with caution in obese individuals, especially in women.

PO2336
Estimated GFR Slope and Risk of Subsequent ESKD in Japanese Patients with CKD: The CKD-JAC Study
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Background: Slope of estimated glomerular filtration rate (eGFR), or rate of eGFR change, is a well-accepted measure of kidney disease progression. Previous studies have shown strong associations between eGFR slope and subsequent ESKD, but there is a dearth of evidence in Asian populations. We aimed to investigate the association between eGFR slope and subsequent ESKD in Japanese patients with CKD using data from the Chronic Kidney Disease Japan cohort (CKD-JAC Study).

Methods: We investigated the association of 2-year change in eGFR (slope) with ESKD over the long term. Slopes were estimated with the linear mixed models with an unstructured variance-covariance matrix, random intercept, and random slope for each individual to estimate slope (mixed model slope) or the least-squares linear regression (least-squares slope). We also conducted sensitivity analyses to investigate the association of 1- and 3-year changes in eGFR with ESKD.

Results: Of the total 2966 participants, we included 2381 individuals after excluding those who were censored within the 2-year baseline period (n = 509) and those with eGFR measured less than twice each year (n = 76). The mean slope was -1.70 ± 2.63 ml/min per 1.73 m² per year when estimated by the mixed-effects model and -1.69 ± 3.18 ml/min per 1.73 m² per year when estimated by least squares. The restricted cubic splines showed that the association between eGFR slope and ESKD was linear. The adjusted hazard ratio for ESKD associated with a lesser eGFR decline by 1 ml/min/1.73m² per year was 0.69 (95% CI: 0.66 to 0.73) for the mixed model slopes and 0.74 (95% CI: 0.71 to 0.77) for the least-squares slope. Sensitivity analysis showed that the association between eGFR slope and ESKD was pronounced when the slope was estimated over a longer baseline period.

Conclusions: Our study confirmed a robust and strong association between eGFR slope and subsequent ESKD in Japanese patients with CKD.

Funding: Commercial Support - Kyowa kinen Co.,Ltd.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Japanese cohort. The study population included patients aged 18 years between 2015-
2020 with two consecutive estimated glomerular filtration rate (eGFR) readings ≥30 and
<60 mL/min/1.73 m² recorded ≥90 and ≤730 days apart. Undiagnosed CKD was defined
as the absence of an associated CKD diagnosis code any time before 12 months prior
to the first eGFR measurement and up to 6 months after the second eGFR. Presence of
recorded urine albumin-to-creatinine ratio (UACR) was also assessed.

Results: After applying the eligibility criteria the study cohorts included 23,160
patients in France and 90,902 in Japan, and the proportions of patients with undiagnosed
S3 CKD were 95.4% (95% confidence interval [CI] 95.1, 95.7) and 92.1% (91.9, 92.3),
respectively. Prevalence in both cohorts was consistent across subgroups stratified by age
(45-65, and ≥65 y), sex, and presence of comorbidities (T2D, HTN, and heart failure)
with the exception of T2D in Japan, where undiagnosed prevalence was 82% (95% CI
81.9, 83.0). Only 2.4% of patients in the cohort in France and 5.5% in Japan had a record of
a UACR value.

Conclusions: The results presented here indicate that a high proportion of early
CKD patients in France and Japan are undiagnosed, with a very low frequency of UACR
testing. With the advent of promising novel therapies to mitigate disease progression
in patients at risk and the potential to improve patient outcomes, a clear imperative exists
to highlight the importance of early CKD detection, diagnosis, and intervention.

Funding: Commercial Support - AstraZeneca

PO2338
Trends in CKD Awareness and Related Clinical and Demographic Characteristics in Korea from 1998 to 2018

Background: Chronic kidney disease (CKD) is a common and growing problem in
Korea. Although CKD awareness is the first step of CKD management, evidence indicates
that the rate of CKD awareness is unsatisfactory worldwide. Thus, we investigated
the trend of CKD awareness for CKD patients in Korea.

Methods: Through analyzing data of Korea National Health and Nutrition
Examination Survey (KNHAES) in 1998 (phase I), 2005 (phase III), 2010-2012 (phase
V), and 2016-2018 (phase VII), we evaluated the rate of CKD awareness according to
CKD stage in each phase of KNHANES. CKD was defined when estimated glomerular
filtration was below 59 ml/min/1.73m². Clinical and sociodemographic characteristics
were compared between CKD awareness and unawareness groups. Multivariate
regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence
interval (CI) for CKD awareness (adjusted OR [95% CI]) in given socioeconomic and
clinical factors.

Results: The overall rate of CKD awareness remained at low levels less than 4.1%
across all phases of KNHANES. In particular, the rate of CKD awareness was remarkably
low in stage 3 CKD. Compared to CKD unawareness group, CKD awareness group was
of young age, higher income, higher education, more medical aid, higher prevalence of
comorbidities, and more advanced CKD. In multivariate analysis, CKD awareness was
significantly associated with younger age (0.95 [0.93-0.98]), medical aid (4.35 [1.95-9.73])
and renal function (0.90 [0.88-0.92]).

Conclusions: The rate of CKD awareness has been consistently low in Korea. This
trend warrants the special endeavor to promote CKD awareness in Korea.

PO2339
Usefulness of Machine-Learning-Predicted Probability as a New Risk Index for Prediction of Renal and Life Prognoses of CKD
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Background: Personalized and accurate prediction is useful for chronic kidney
disease (CKD) therapy. Predialysis death is a competitive risk of dialysis in CKD patients
and lowers the accuracies of the prediction of their renal and life prognoses. Thus, we
determined whether machine-learning-predicted probability works as an index for the
risks of predialysis death and dialysis in CKD patients and attempted its application.

Methods: We constructed a database of electronic-medical-record data of CKD
patients in Japan, and developed risk prediction machine-learning models using random
forest (RF), Gradient Boosting Decision Tree, and eXtreme Gradient Boosting for the
prediction of dialysis and death over 1 year. The performances of the probabilities
estimated using the models were compared by the bootstrap method with those of clinical
indices in a prospective cohort study of CKD patients (n=67,957).

Results: Sixteen models were developed and showed statistically significantly higher
C-statistics than clinical indices. Two RF models including 22 or 8 variables showed high
C-statistics: 0.932 (95% CI 0.916, 0.948) and 0.95 (0.915, 0.945), respectively, which were
higher than estimated glomerular filtration rate and urinary protein levels (p<0.0001). Cox
proportional hazards models with the spline term showed the relationship between the
high probabilities and the high outcome risks (p<0.0001). We also developed a Web-based
risk prediction system using those two models.

Conclusions: This study showed that the machine-learning-based probability is
useful as a new risk index for dialysis and death and applicable to clinical practice.

PO2340
A Machine Learning Algorithm to Identify Patients with Possible Non-Dialysis-Dependent CKD
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Hospitalier de la Côte Basque, Bayonne, France; 5Astellas Pharma Europe B.V., Leiden, Netherlands.

Background: The DAKOTAH study is a retrospective study of patients with non-
dialysis-dependent chronic kidney disease (NDD CKD) in France based on data from the
Echantillon Généraliste des Bénéficiaires database. A stepwise machine learning approach
was used to identify patients with possible NDD CKD who could not be captured using
the NDD CKD case definition (Figure).

Methods: First, the ‘potential CKD’ population was designated as patients with a
diagnosis of diabetes, cardiovascular disease or hypertension, or with at least 3 prescriptions
for antidiabetic and/or antihypertensive drugs, during 2012–2017. Second, an unsupervised
algorithm was trained to identify patients very likely to have CKD (‘possible CKD’) in
the potential CKD population. Similarity between patients was based on CKD-related
variables: sex, number and duration of hospitalizations for renal failure, number of GP

CKD prevalence in Korea from 1998 to 2018

CKD awareness in Korea from 1998 to 2018

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
visits; medications; and biological exams. A distance metric between patients was defined based on these variables, and patients having similar characteristics were positioned close to one another. The algorithm learned to construct a spherical boundary around the non-CKD population, to create a decision rule for possible CKD versus non-CKD, with outliers considered possible CKD.

Results: The algorithm was validated by application to both the potential CKD population and a confirmed CKD patient pool. From the potential and confirmed CKD populations, 21% and 65% of patients were classified as possible CKD, respectively. Similarities were observed between the two groups regarding hospitalizations and selected biological exams.

Conclusions: This machine learning-derived decision rule could be a tool to identify undiagnosed patients with NDD CKD.

Funding: Commercial Support - Astellas Pharma Inc.

PO2341

Developing an Electronic Health Record (EHR)-Based Model for Delineating Advanced CKD Cohort in Veterans Affairs (VA) System

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Background: Late diagnosis of chronic kidney disease (CKD) and non-referral to nephrology are important limiting concerns for pre-end stage kidney disease (ESKD) nephrology care, including dialysis modality evaluation. Querying existing electronic database with longitudinal patient-level data can improve recognition of advanced stage 4/5 CKD and facilitate evidence-based pre-ESKD care. Using a mixed approach of electronic query followed by manual chart review, we report the development of an Electronic Health Records (EHR)-based model that allows identification and quantification of advanced CKD burden in a regional Veterans Healthcare System (VHS).

Methods: We identified all Veteran enrollees at a large regional VHS using VA Informatics & Computing Infrastructure data set. Among these, we identified all Veterans with an eGFR below 30 ml/min or an existing ICD-10 diagnostic code for stage 4/5 CKD within last 12 months. We applied diagnostic and procedure codes for dialysis, ESKD, and acute kidney injury (AKI) in an iterative approach to improve the accuracy of identifying non-diagnosis advanced CKD cohort.

Results: Of 148,164 active enrollees within VHS, our initial model of using a single eGFR <30 ml/min identified 3,813 (2.57%) Veteran enrollees with advanced CKD. Manual review of a select cohort (n=787) showed 63.3% error rate, with high rates of ESKD and AKI being major confounders. Successive iterations involved exclusions of ESKD and AKI codes and incorporation of a second latest eGFR >90 days before latest eGFR. The final EHR-based advanced CKD model included 1,326 (0.89%) Veterans with the residual error of 14.4% on manual chart review without the possibility of further automated exclusions. Of these, 882 were found to have definite advanced CKD and 457 were classified as probable advanced CKD based on whether both or only one of the latest two eGFRs more than 90 days apart were below 30 ml/min with CKD.

Conclusions: An EHR-based model to identify advanced CKD can be successfully developed for a regional VHS with over 85% accuracy. Further testing is needed to determine its wider applicability across additional VHA sites, and if validated, this model can be applied across the VHA electronic data to identify the burden of advanced CKD for needs assessment and clinical care among Veterans.

Funding: Veterans Affairs Support

PO2342

Developing a Prediction Model for Incidence of Newly Detected CKD Among US Veterans, 2009-2018

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Background: Both screening and awareness of CKD remain low in the US. We sought to develop a tool to aid physicians and health systems in identifying patients most likely to develop CKD, using a large national sample of patients in the Veterans Health Administration (VHA).

Results: Of 29,524,195 observations from Veterans, aged 18+ with outpatient creatinine data (2006-2018), we modeled the probability of newly detected CKD using discrete survival methods. Veterans were screened for 2-3 years to ensure no pre-existing CKD. Newly detected CKD was defined as a diagnosis or by laboratory measurement (eGFR <60 ml/min/1.73m2 or UACR 30+ mg/g). Predictors included demographics, comorbidities, nephrotoxic medications, and laboratory values updated each year. Model fit assessed by the c-statistic.

Results: The cohort had a mean age of 59 years with 89% males and 15% Black race. The average eGFR was 87 ml/min/1.73m2 and median UACR was 8 mg/g, with an average of 3.9 years follow-up. The largest predictors of incident CKD were diabetes, kidney stones, urinary tract infections, sickle cell anemia, and an eGFR between 60-69 ml/min/1.73m2. Concordance was high (c-statistic=0.84, Fig: ROC curve). Using a threshold of 3% risk for screening would require testing 1/3 of Veterans (~1 million per year), yielding an 83% true positive and a 17% false negative rate.

Conclusions: We are able to accurately predict the probability of incident CKD in the VHA. This predictive model has the potential for improving targeted screening efforts for CKD, facilitating its earlier detection, raising awareness, and reducing disparities. If externally validated, the impact of these findings would be generalizable to populations/health systems beyond the VHA.

Funding: Veterans Affairs Support

PO2343

A Population Health Survey-Based Prediction Equation for Incident CKD: The CKD Population Risk Tool CKDPORT/PREDICT-CKD LIFESTYLE

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Background: Chronic kidney disease awareness among the general public is less than 10%. Patients’ health behaviours are known to be associated with CKD development and disease progression. Prediction tools that engage the general public with their self-reported health information could increase awareness, identify modifiable lifestyle risk factors, empower patients, and prevent disease. The study objective was to develop and validate a population health survey-based prediction equation to determine the risk of incident CKD in the general public.

Methods: Participants: Completed the Canadian Community Health Survey (CCHS) were linked to laboratory and hospital admission data between 2000 and 2015 in Ontario, Canada. The primary outcome was incident CKD (eGFR <60 ml/min/1.73m2) with up to 8 years of follow-up. Models accounted for the competing risk of all-cause mortality. The CCHS is a random, comprehensive, prospective, general population survey that captures information on demographics, co-morbid illnesses, lifestyle and behaviours, diet, body mass index and mood. External validation was performed using data from the UK Biobank.

Results: From 22,200 eligible adults, 1,981 (8.9%) developed incident CKD during a mean follow-up time of 8 years. Domains included in the final reduced model were baseline eGFR, smoking, alcohol, physical activity, education, mood, fruit and vegetable intake, diabetes, hypertension, heart and lung disease, urinary incontinence, cancer, and BMI. The model demonstrated excellent discrimination in individuals with and without a baseline eGFR measure (5-year c-statistic with baseline eGFR: 0.84 95% CI 0.82-0.85, without 0.81 95% CI 0.80-0.82), was well calibrated (Brier score at 5-years with baseline eGFR: 0.07 95% CI 0.00-0.08, without 0.08 95% CI 0.07-0.08), and was consistent in a sensitivity analysis using 2 measures of eGFR >90 days apart to define the outcome. The model was consistent with external validation.

Funding: UK Biobank

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: Lifestyle and health behaviour in people from population-based health surveys can predict incident CKD in the population with excellent discrimination and can be used to improve public engagement in CKD awareness.

PO2344

Predicting ESKD Risk and Time to RRT Initiation Based on Past Slope and Current Value of eGFR: The CKD-JAC Study

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Background: Past slope and current estimated glomerular filtration rate (eGFR) are used to predict future risk of end-stage kidney disease (ESKD) and time to renal replacement therapy (RRT) initiation in clinical practice, but there is limited quantitative evidence supporting this practice. To address this, we analyzed data from the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study.

Methods: We investigated the association of 2-year eGFR slope estimate, estimated using linear mixed models, with subsequent risk of ESKD using Cox regression models adjusting for eGFR and other potential confounders collected 2 years after cohort entry. We calculated the net reclassification improvement (NRI) to assess whether adding past slope to age, sex, eGFR, and urine albumin-to-creatinine ratio (UACR) improves ESKD risk prediction. We predicted time to RRT initiation based on the past slope and current eGFR, assuming eGFR of 6 mL/min/1.73m2 to be the timing of RRT initiation, and compared it with actual time to RRT initiation.

Results: We included 2381 participants who had survived free of ESKD for 2 years and with eGFR measurements at least twice each year. The mean 2-year eGFR slope was 1.70 ± 1.63 mL/min per 1.73 m2 per year. During a median follow-up of 4.7 years after the 2-year sleep evaluation period, 175 participants died and 810 reached ESKD. Reassessing Race and Predicting Progression

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Gallardo,1 Huanguang

 aggregate outstanding need for VA-preferred SRC and CPE were 14 (15%) and 69 (73%) respectively. There were significant differences in needs and preferences across the respondents albeit, 40 (50%) received renal care from non-VA providers. Among respondents, 74 (87%) with advanced CKD. Of the 226 Veterans randomly selected mail-invites, 166 made participation. Surveys were conducted for those agreeable for mail-invited Veterans with up to three attempted calls for those who do not call back. Following a random order, and manual review of randomly selected EHRs, we created a model for isolating current state of and outstanding needs and preferences for SRC and CPE at North Florida/South Georgia Veterans Health System. We then sorted the cohort in a random order, and train and validate the prediction model. The dataset was generated by using Synthea®, a patient generator tool, and contains standard data elements that are commonly used in major Electronic Health Record systems. A total of 12,503 patients with CKD and 18,212 patients without ESKD matched by propensity score along with 290 other features including anthropometrics, medication, comorbidities, and laboratory data were used to train and validate the prediction model. Results: The CNN algorithm has been designed, implemented and tested using the synthetic dataset, achieving precision of 0.918, recall of 0.739, specificity of 0.983, accuracy of 0.932, and AUROC of 0.937 as depicted in Figure 1. Additionally, based on the dataset, age, diabetes, elevated BMI and medication taken, specifically 24 HR Metformin Hydrochloride, represent the topmost important features to predict the onset of CKD.

Conclusions: Using CNN and synthetic veteran patient dataset, we have demonstrated a viable prediction model for CKD detection in healthy patients at-risk of CKD using longitudinal data from Electronic Health Records (EHR). The prediction model can be easily deployed in a CKD screening program in healthcare institutions with existing EHR systems.

Funding: Veterans Affairs Support

PO2346

Artificial Intelligence-Based Prediction Model for Screening Veteran Patients at Risk of Developing CKD

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Background: Developing effective screening tools for Chronic kidney disease (CKD) helps in reducing morbidity, mortality as well as cost and burden to the health system. Here we present preliminary result on feasibility and performance of employing Convolutional Neural Network (CNN) prediction model in detecting patients who are at-risk of CKD based on longitudinal data from Electronic Health Records (EHR).

Methods: A synthetic dataset containing a total of 100,000 synthetic patient records, derived from cross-sectional cohort of Veteran from the general population, was used to train and validate the prediction model. The dataset was generated by using Synthea®, a patient generator tool, and contains standard data elements that are commonly used in major Electronic Health Record systems. A total of 12,503 patients with CKD and 18,212 patients without ESKD matched by propensity score along with 290 other features including anthropometrics, medication, comorbidities, and laboratory data were used to train and validate the prediction model.

Results: The CNN algorithm has been designed, implemented and tested using the synthetic dataset, achieving precision of 0.918, recall of 0.739, specificity of 0.983, accuracy of 0.932, and AUROC of 0.937 as depicted in Figure 1. Additionally, based on the dataset, age, diabetes, elevated BMI and medication taken, specifically 24 HR Metformin Hydrochloride, represent the topmost important features to predict the onset of CKD.

Conclusions: Using CNN and synthetic veteran patient dataset, we have demonstrated a viable prediction model for CKD detection in healthy patients at-risk of CKD using longitudinal data from EHR system. The prediction model can be easily deployed in a CKD screening program in healthcare institutions with existing EHR systems.

Funding: Veterans Affairs Support

PO2347

Identifying Hotspots of CKD in the United States with Data from a Large National Clinical Laboratory Network

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Background: CKD is typically detected through routine laboratory testing. We sought to assess the feasibility of analyzing data from one of the largest clinical laboratory networks in the US to map CKD hotspots across the nation.

Methods: Laboratory results for serum creatinine were analyzed from a nationally standardized laboratory platform with the Laboratory Corporation of America (Labcorp) across 3-month period (July to December 2019, n=21,884,579). We assessed the percent of results with eGFR <60 mL/min/1.73 m2 (CKD stages 3-5) at US county-level (n=2,972 counties, <11 results supressed). Due to lack of race information, the CKD-Epi equation without the race coefficient was employed for the entire population. Hotspot analyses were conducted using the Getis-Ord Gi* statistic.

Results: The total population was 44% male with mean age of 56 years. eGFR results <60 mL/min/1.73 m2 totalled 4,165,540 (19%) and county-level distribution ranged from 0% to 75% (Fig. A) with an overall mean age of 72 and 44% male. Results of the hotspot analysis (Fig. B) shows the percent of decreased kidney function varies markedly across

Figure 1: Onset of CKD Prediction Metrics

PO2345

Need and Preference Assessments for Renal Care and Comprehensive Pre-ESKD Education Services for Advanced CKD Veterans

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Background: Current guidelines suggest Specialty Renal Care (SRC) and comprehensive pre-end-stage kidney disease (ESKD) education (CPE) Services for all patients with advanced, stage 4-5 chronic kidney disease (CKD). Despite this, half of incident ESKD patients receive none or <6-months pre-ESKD renal care. Estimating outstanding needs and understanding Veterans preferences for receiving such care can improve recent source allocations and quality of Veterans Affairs Health Administration (VAHAI).

We conducted a community-based evaluation of advanced CKD Veterans to assess their current state of and outstanding needs and preferences for SRC and CPE at North Florida/South Georgia (CFG) VA HAI system.

Methods: Through an iterative approach of electronic health records (EHR) query followed by manual review of randomly selected EHRs, we created a model for isolating advanced CKD cohort at NF/SG HAI. We then sorted the cohort in a random order, and mail-invited Veterans with up to three attempted calls for those who do not call back to actively opt-out of participation. Surveys were conducted for those agreeable for participation.

Results: Of the 148,164 active enrollees, we identified 1329 (0.9%) Veterans with advanced CKD. Of the 226 Veterans randomly selected mail-invites, 166 made final contact; 94 completed, 50 asked for more time, and 22 refused to participate in the surveys. Awareness of CKD (91%) and prevalence of renal care (86%) were high among respondents albeit, 40(50%) received renal care from non-VA providers. Aggregate outstanding need for VA-preferred SRC and CPE were 14(15%) and 69(73%) respectively. Among those with preferences for receiving SRC were 66(43%) & 80(57%) and receiving CPE were 21(30%) & 34(50%) through in-person and telemedicine-based care respectively. There were significant differences in needs and preferences across the socio-demographics and rural-urban spectrum.

Conclusions: Despite high awareness of CKD diagnosis and prevalence of SRC, there is significant outstanding need for targeted CPE services in advanced CKD Veterans. Further validation of this model at additional VHAs and its application across the system can allow projection of outstanding needs for SRC and CPE across the VHA and guide appropriate allocation of resources to improve Veteran outcomes.

Funding: Veterans Affairs Support
the US, with clear hot spots in the south and southeast, far northeast, Pacific Northwest, Missouri, Colorado, and Utah. The upper midwest and most of the northeast appeared as cold spots, with the southwest being neither a hot nor cold spot.

**Conclusions:** We demonstrate the feasibility of leveraging a large national laboratory network database for mapping the distribution of county prevalence of CKD and identification of CKD hotspots. Ongoing work is focusing on understanding factors underlying these hotspots and will help guide population health improvement, raise awareness, guide health policy and direct public health action and quality improvement efforts related to kidney disease.

**Funding:** Commercial Support - Laboratory Corporation of America Holdings

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**PO2349**

A Systematic Literature Review of Treatment Patterns, Profiles, and Long-term Disease Progression in Patients with CKD and Type 2 Diabetes Mellitus

**Rakesh Singh,**1 Erika Wissinger,2 Casey Dobie,2 Yuxian Du1

**Bayer US LLC, Whippany, NJ; 2Acenda LLC, Carrollton, TX**

**Background:** CKD affects ~40% of patients with diabetes. Current guidelines recommend optimization of blood pressure and glycemic control in patients with T2D to reduce the risk of CKD progression. Despite this, patients with T2D are still at risk for ESRD. Real-world treatment patterns, safety profiles of current treatments, and residual risk for long-term disease progression in patients with CKD and T2D were explored.

**Methods:** A systematic literature review was conducted of real-world observational studies in the US in patients with CKD and T2D. Articles published in the past 10 years were identified from Embase and MEDLINE and were evaluated by 2 independent reviewers.

**Results:** A total of 17 studies were included in the review. In the 16 studies that examined treatment patterns among patients with CKD and T2D, all drug classes of interest (steroidal mineralocorticoid receptor antagonist [MRA], ACEI, ARBP, GLP-1RA, and SGLT-2i) were reported. The proportions of patients treated with ACEIs (34%–70%) or ARBs (12%–68%) varied widely, with approximately 45% to 95% of patients prescribed either an ACEI or an ARB. Small proportions of patients (~10%) were treated with MRAs, GLP-1RAs, and SGLT-2is; though steroidal MRA does not have an indication in CKD in T2D. In the 4 studies that examined renal function decline while on a treatment of interest, 1-year progression rates ranged from 3.3% to 29.9%. Three studies reported rates of on-treatment ESRD progression, which ranged from 9.1% to 10%. In the 4 studies reporting AEs in patients treated with MRAs, ACEIs, and/or ARBs, notable clinical events included stroke (12.6% among MRA non-users to 31.3% among spironolactone users) and hyperkalemia (9.1% among MRA non-users to 29.9% among spironolactone users).

**Conclusions:** The identified studies suggest that patients with CKD and T2D may not be optimized on current treatment options to slow renal function decline and reduce the risk of CV events in these patients. Despite current treatment options, a residual risk of CKD progression and CV morbidity remains. New therapies are needed to slow long-term disease progression.

**Funding:** Commercial Support - Bayer US LLC

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**PO2350**

International Variation in the Incidence of Kidney Failure in the CKDopps

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**Background:** Data from kidney replacement therapy (KRT) registries suggest large international variation in the incidence of kidney failure (KF). However, these data strongly depend on treatment availability and practices of KRT initiation. Measuring the incidence of sustained low eGFR, i.e. <15 mL/min/1.73 m², would enable to explore differences in progression to KF across countries after adjusting for individual characteristics.

**Methods:** We analyzed data from patients with CKD stages G3-G4, under nephrology care in representative samples of clinics in Brazil (n= 747), France (n= 2786), Germany (n= 2539), and the United States (n=1309), participating in the CKDopps. We used Weibull PH models to compare the risk of KRT initiation across countries, and Illness-death models for interval censored data, to compare the risk of sustained low eGFR and to estimate probabilities of KF (composite of KRT initiation and sustained low eGFR).

**Results:** Median age (years) ranged from 67 in Brazil to 75 in Germany, mean baseline eGFR (mL/min/1.73m²) from 27 in Germany to 33 in France; male sex from 52% in the United States to 66% in France. After a median follow-up of 4.0 (2.6-5.0) years, 1648 patients met a sustained low eGFR, and 1343 initiated KRT. Compared with the United States, the adjusted hazard ratios indicated 44% lower risk of KRT initiation in France (HR 0.56 95% CI 0.39 to 0.79), similar risk in France (1.05, 95%CI 0.83 to 1.33), and 41% higher risk in Germany (95% CI 1.12 to 1.77). The same pattern was observed for sustained low eGFR, but differences were narrowed. Two-year cumulative probability of KF ranged from 13% in Brazil to 16% in Germany (Figure)

**Conclusions:** The incidence of KF varies across CKDopps countries, but to a much lesser extent than the incidence of KRT initiation. This finding highlights the relevance of such approach to disentangle the effects on CKD progression from those on care.

**Funding:** Commercial Support - Akebia Therapeutics, Inc.; Argenx Inc (since 1996, founding sponsor); AstraZeneca Pharmaceuticals LP; Bard Peripheral Vascular, Inc.; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical Co., Ltd; Dialyze Direct, LLC; Fresenius Medical Care Asia-Pacific Ltd; GlaxoSmithKline LLC; Japanese Society for Peritoneal Dialysis; JMS Co., Ltd.; Kidney Research UK Kidney Foundation Japan; Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corpor; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Sanofi-Aventis Deutschland GmbH; Terumo Corporation •Torii Pharmaceutical Co., Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd, Government Support - Non-US
PO2351

Development and Validation of an Algorithm to Predict Risk of 90-Day Hospitalization for Patients with CKD

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Background: Patients with chronic kidney disease (CKD) are at higher risk of being admitted to the hospital than the general population. Hospitalizations in CKD patients are often associated with higher medical costs, increased morbidity, and increased risk of transition to end-stage kidney disease (ESKD). Nationally, there seems to be an increasing focus on the management of CKD upstream of ESKD. Identification of CKD patients at greatest risk of hospitalization may hold promise to improve clinical outcomes and judicious allocation of health care resources.

Methods: This model was developed using Medicare Part A and Part B claims from calendar years 2017-2019. Data from 50,000 unique patients diagnosed with CKD stages 3-5, no evidence of ESKD, or claims for dialysis were split into derivation (n = 40,000) and validation (n = 10,000) sets. The predicted outcome was all-cause hospital admissions, which occurred in 10.4% of patients 90 days after scoring. Overall performance of candidate models was assessed using area under the curve (AUC) of the receiver operating curve in addition to positive predictive value (PPV) and sensitivity across a variety of thresholds.

Results: The best model that we tested was a gradient boosting machine algorithm based on 399 input terms, which represented 147 unique clinical constructs. The model demonstrated good ability to discriminate (AUC = 0.73), which was stable when tested in a validation set (AUC = 0.73). The PPV in the validation set was 30.6%, 24.0%, and 21.6% at the 10%, 20%, and 30% thresholds, respectively. The sensitivity in the validation set was 28.8%, 45.3%, and 60.9% at the 10%, 20%, and 30% thresholds, respectively.

Conclusions: We developed an algorithm that uses only information derived from medical claims to identify CKD 3-5 patients at highest risk of being hospitalized in the near-term. This algorithm could be used as a decision support tool for clinical programs focusing on the management of CKD patient populations.

PO2352

CKD and Risk of Incident Hospitalization with Clostridioides difficile Infection: Findings from the Atherosclerosis Risk in Communities Study Junichi Ishigami,1 Keichi Sumida,2 Morgan Grams,3 Alex R. Chang,4 Pamela L. Lutsey,5 Andrew S. Levey,5 Josef Coresh,5 David W. Dowdy,6 Kunihiro Matsushita.1 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 2The University of Tennessee Health Science Center College of Medicine, Memphis, TN; 3Johns Hopkins Medicine, Baltimore, MD; 4Geisinger Health, Danville, PA; 5University of Minnesota Twin Cities, Minneapolis, MN; 6Tufts Medical Center, Boston, MA.

Background: Clostridioides difficile (C. difficile) infection is a major public health priority in the US. Individuals with CKD are at high risk of hospitalization and infection in general; however, the association of CKD with the risk of C. difficile disease has not been systematically evaluated.

Methods: We evaluated data from 11,017 participants of the ARIC Study (mean age, 63 years; 56% female; 22% Black) to explore the association of CKD with the risk of incident hospitalization with C. difficile infection. We categorized the study population into four risk categories defined by eGFR and ACR. CKD was defined as eGFR <60 ml/min/1.73m2 or ACR ≥30 mg/g, and no CKD was defined as low risk. CKD was subdivided into moderate, high, and very high risk. Adjusted HRs were estimated using Cox regression models.

Results: During a median follow-up of 20.1 years, 309 participants had incident hospitalization with C. difficile infection. In multivariable Cox regression analysis, there was a graded association of CKD risk category with the risk of hospitalization with C. difficile infection, with adjusted HRs of 4.74 [2.29 to 10.23] for CKD with very high risk, 2.33 [1.39 to 3.90] for CKD with high risk, and 1.34 [0.93 to 1.93] for CKD with moderate risk compared to no CKD (P-for-linear-trend, <0.001) (Figure 1). These findings were consistent in subgroup analyses and sensitivity analyses, including analyses that accounted for frequency of prior hospitalization and for the risk of hospitalization itself.

Conclusions: In this community-based cohort, CKD was associated with the risk of hospitalization with C. difficile infection. Individuals with CKD should be a key target population for public health initiatives and clinical approaches to prevent C. difficile infection.

PO2353

Lower Serum Bicarbonate Is a Risk Factor for Hospitalization for Infection Among Patients with CKD

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Background: Hospitalization due to infection is common in patients with CKD; both lower eGFR and albuminuria are risk factors. Metabolic acidosis impairs neutrophil function in ESRD patients via delayed apoptosis, enhanced phagocytosis, and increased oxidative burst reactions, however serum bicarbonate has not been investigated as a risk factor for infection in patients with non-dialysis CKD.

Methods: We utilized a central data warehouse from Mass General Brigham for patients with ≥1 diagnostic code for CKD between 2010-2020. CKD was defined as 2 outpatient eGFR values <60 mL/min/1.73m2 at least 3 months apart. Patients were excluded if they had a kidney transplant, a humoral immunodeficiency, or ESRD on dialysis prior to index date. The primary outcome was hospitalization for infection (defined by primary diagnosis of urinary tract infection/ pyelonephritis, pneumonia, cellulitis, or bacteremia). We examined outpatient baseline serum bicarbonate and risk of hospitalization for infection using Cox proportional hazards models adjusting for potential confounders. Patients were censored at time of first infection, last lab value, or death.

Results: We included 36,647 patients with CKD, and 8,521 were hospitalized for infection. When adjusting for covariates, the risk for infection increased as serum bicarbonate decreased (Figure 1). A serum bicarbonate of <20 mEq/L compared to ≥28 mEq/L was independently associated with an 18% (95% CI 1.03-1.32) higher risk of hospitalization. In the adjusted model, CKD stage 5 was associated with a 69% (95% CI 1.47-1.94) increased risk of infection compared to CKD stage 3a. Albuminuria ≥300 mg/g was associated with a 28% (95% CI 1.14-1.44) increased risk of composite infection compared to <10 mg/g.

Conclusions: Our findings suggest that clinicians should consider lower serum bicarbonate a risk factor for infection in patients with CKD. Future studies should explore whether bicarbonate supplementation can reduce risk of infection.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2354

Albuminuria Testing in Hypertension and Diabetes
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Background: Albuminuria is an under-recognized component of chronic kidney disease (CKD) definition, staging, and prognosis. Despite significant advances in therapies for patients with albuminuria, guidelines, particularly for hypertension, conflict on recommendations for urine albumin-to-creatinine ratio (ACR) measurement.

Methods: We separately analyzed 3,055,841 adults with diabetes in 25 cohorts and 2,111,587 non-diabetic adults with hypertension in 21 cohorts from the CKD Prognosis Consortium. We estimated ACR testing rates during a 2-year window, and developed and utilized risk prediction models for prevalent albuminuria (ACR ≥ 30 mg/g) to determine if high-risk patients for albuminuria are more likely to be tested and to estimate the burden of undetected albuminuria.

Results: Overall, the ACR testing rate was 35.3% in diabetes and 4.1% in hypertension. Among patients with diabetes, testing rates varied greatly across the different health systems and were largely unrelated to the predicted risk of prevalent albuminuria (Figure A). Among patients with hypertension, testing rates were low and also unrelated to the predicted risk of prevalent albuminuria (Figure B). The estimated ratio (cohort range) of undetected (due to lack of testing) to detected prevalent albuminuria was 1.8 (0.2-7.6) in diabetes and 19.5 (0.8-78.3) in hypertension.

Conclusions: Real-world ACR testing is low, particularly among non-diabetic patients with hypertension, and testing is unrelated to predicted risk. There are large swaths of the population with diabetes or hypertension with undiagnosed CKD, suggesting that regular screening for proteinuria is essential for early detection of CKD and appropriate initiation of treatment with cardiovascular and kidney benefits.

Funding: NIDDK Support, Private Foundation Support

PO2355

Increasing Proteinuria Screening to Reduce CKD Progression in High-Risk Patients
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Background: Chronic Kidney Disease (CKD) affects 15% of the US population and is underrecognized by patients and clinicians. Screening for proteinuria is essential in prompting primary care doctors (PCPs) to initiate treatments proven to decrease progression to end stage renal disease, cardiovascular events and mortality in these patients. However, screening rates remain low – one study showed only 13% of adults with CKD had proteinuria/albuminuria testing. Our objective was to identify the high-risk patients with CKD who did not receive annual proteinuria testing, with the long-term goal of addressing barriers to quality care.

Methods: We identified 4214 patients between October and December 2020 within our healthcare system who had a diagnosis of CKD 3 or 4 and categorized them as having diabetes/not having diabetes and having hypertension/not having hypertension. We then assessed how many patients had proteinuria testing in the last year, which included a urinalysis, urine protein to creatinine ratio or urine microalbumin.

Results: Results showed that 100% of patients with diabetes had screening in the last year regardless of CKD stage or hypertension (HTN). For those with CKD3A-HTN only 14% (171/1226) had screening in the last year and for those with CKD3B-HTN only 28% (98/347) had screening in the last year. For patients with CKD3A and CKD3B (without HTN/diabetes), 14% (125/892) and 34% (48/142) respectively had appropriate screening.

Conclusions: Within our large, integrated healthcare system, rates of proteinuria screening in diabetic patients were strikingly high. In contrast, most patients with CKD3 and HTN did not receive testing in the last year. One explanation for this is the workflow in place to help PCPs manage their patients with diabetes, which includes automated reminders and a dedicated multidisciplinary team. Applying a similar systematic, protocol-based workflow to all patients with CKD may help to increase screening rates and improve overall quality of care.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2357

Major Cardiovascular Events and Subsequent Risk of Kidney Failure: A CKD Prognosis Consortium Study

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Chronic Kidney Disease Prognosis Consortium CKD Prognosis Consortium, Baltimore, MD.

Background: Chronic kidney disease (CKD) increases risk of cardiovascular disease (CVD). However, less is known about how CVD is associated with future risk of kidney failure. We quantified the association of incident major CVD events with subsequent risk of kidney failure requiring replacement therapy (KFRF).

Methods: We analyzed data on 18,671,338 individuals from 80 cohorts in the CKD Prognosis Consortium with baseline eGFR and CVD data. We assessed impact of incident coronary heart disease (CHD), heart failure (HF), atrial fibrillation (Afib) and stroke events as a time-varying exposure on the outcome of KFRF in Cox proportional hazard models.

Results: Mean age was 55 years and mean eGFR was 88 ml/min/1.73m², 57% were women, 9% were black, 12% had diabetes and 30% had ACR available (median 13 mg/g); 9% had prevalent CHD, 3% HF, 2% Afib, and 4% prior stroke. During follow up there were 175,886 CHD, 480,963 HF, 428,419 Afib and 211,423 stroke incident events and 85,513 (0.5%) patients required KFRF. Each CVD event increased the adjusted hazard ratio (HR) for subsequent KFRF (Table). The increased hazard was highest in the first year after CVD incidence and attenuated thereafter. HRs were modestly weaker at lower eGFR. HF showed the strongest association before and after adjustment for other CVD subtype incidence. Absolute risk of KFRF associated with incident CVD after accounting for competing risk of mortality was higher for lower baseline eGFR and higher ACR, with 2-year KFRF risk of 25%, 28% and 20% for CHD, HF, Afib and stroke in subjects with eGFR 15-29 ml/min/1.73m² and ACR >300 mg/g.

Conclusions: Incident CVD events are strongly and independently associated with risk for KFRF, with greatest risk in the first year following HF, then CHD and stroke. These data highlight need for greater awareness of KFRF risk following CVD events. Specific strategies to elucidate mechanisms and test interventions to reduce the KFRF risk post CVD events warrant investigation.

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PO2358

Bidirectional Association Between Kidney Function and Atrial Fibrillation in the General Population

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Background: A potential bidirectional relationship between kidney dysfunction and atrial fibrillation (AF) has been suggested, but has not been studied in the general population. Therefore, we aimed to study the association of different assessments of kidney function with prevalent and incident AF in the general population.

Methods: Participants aged 45 years from the Rotterdam Study, a population-based cohort study, with information on kidney function and AF were included. Assessments of kidney function included single assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcreat), serum cystatin C (eGFRcys), or both (eGFRcreat-cys), annual assessments with eGFRcreat-cys, serum albumin (A CR), and repeated assessments of eGFRcreat. Incident chronic kidney disease (CKD) was defined as the first time eGFRcreat dropped <60 ml/min per 1.73 m². Cox-proportional hazards, logistic regression, linear mixed, and joint models were used to investigate the associations of eGFR with incident and prevalent AF. Absolute 10-year risk of AF was computed using a competing risk analysis. All models were adjusted for potential confounders including cardiovascular risk factors.

Results: During a median follow-up time of 8.0 years, 780 incident AF cases occurred in 5,128 participants (mean age 64.9 years, 57.2% female). Lower eGFRcreat and eGFRcreat-cys were significantly associated with an increased risk of incident AF (hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.03-1.14 and HR 1.07, 95% CI 1.01-1.14, respectively, per 10 ml/min per 1.73 m² decrease in eGFR), while eGFReat was not. No association between urine ACR and incident AF was found. Absolute 10-year risk of developing AF increased from 4.9% to 7.1%, when comparing eGFReat values of 90 to 60 ml/min per 1.73 m². Prevalent AF (409 cases) was associated with an average 2.85 ml/min per 1.73 m² lower eGFReat values over time and furthermore, a faster decline of eGFReat with aging was revealed when compared to participants without prevalent AF. Prevalent AF was also associated with a 1.3 fold increased risk of incident CKD.

Conclusions: Kidney function and AF are bidirectionally associated. This insight may be used to improve prediction and prevention of both conditions, for example through targeted screening programs in the general population.

PO2359

Longitudinal Ankle Brachial Index and Risk of CKD Progression

Kirsten S. Dorans,1 Jing Chen,22 Xingyan Li,1 Hua He,1 Jordana B. Cohen,2 Alan S. Go,2 L. Lee Hamm,2 Edward J. Horwitz,2 Bernard G. Jaar,1 James P. Lash,2 Rupal Mehta,2 Sylvia E. Rosas,2 Anand Srivastava,2 Jonathan J. Taliercio,12 Jiang He,12 CRIC Study Investigators 1 Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; 2Tulane University School of Medicine, New Orleans, LA; 3University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4Kaiser Permanente Northern California, Oakland, CA; 5Johns Hopkins Medicine, Baltimore, MD; 6University of Illinois at Chicago, Chicago, IL; 7Northwestern University Department of Medicine, Chicago, IL; 8Joslin Diabetes Center, Boston, MA; 9MetroHealth Medical Center, Cleveland, OH; 10Cleveland Clinic, Cleveland, OH.

Background: Individuals with chronic kidney disease (CKD) are more likely than the general population to have low or high ankle brachial index (ABI). Low ABI is a predictor of adverse outcomes in CKD, but the relationship of ABI with renal outcomes in CKD is not well studied. As ABI is a simple noninvasive measure, it is important to better understand how ABI relates to CKD progression.

Methods: We carried out a prospective study of 3216 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study without clinical peripheral arterial disease. We used Cox proportional hazards regression to test the associations of baseline ABI and of cumulative average ABI with risk of CKD progression (50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD)) and with risk of ESRD, adjusting for important confounding factors. ABI was measured at annual visits. The shapes of the relationships of exposures with outcomes were assessed with restricted cubic splines.

Results: At baseline, average age was 57.8 years and average eGFR was 44.8 ml/min/1.73m². During follow-up, 1297 individuals had CKD progression (median follow-up 6.9 years, 7 ABI measurements) and 1049 developed ESRD (median follow-up 10.8 years, 6 ABI measurements). In multivariable-adjusted models, there were U-shaped associations of baseline ABI with CKD progression and with ESRD (p for curves <0.001). In models adjusted for baseline ABI, similar U-shape relationships were observed for the associations of cumulative average ABI with CKD progression and with ESRD (p for curves <0.001; Figure).

Conclusions: This study indicates that both high and low ABI are associated with increased risk of CKD progression and ESRD and that even after adjustment for baseline ABI, repeated measures of ABI averaged over time are associated with CKD progression and ESRD. These findings suggest that ABI can be used to facilitate risk stratification for CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences
PO2360

Urinary Peptidome Analysis to Predict the Risk of CKD Progression to Kidney Failure

Joachim Sushrut Paul

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**Background:** Urinary peptidomics (UP) has emerged as one of the most attractive areas in the identification of biomarkers for characterizing CKD but its potential to predict the risk of CKD progression has not been fully investigated. The aims of the present study were to explore if a UP signature can improve the prediction of kidney failure (KF), compared to the risk factors (RF) included in the KF risk equation.

**Methods:** Within the Chronic Kidney Disease-Renal Epidemiology and Information Network prospective cohort of patients with CKD stage G3-G5 (N=3033), we conducted a case-cohort study of 892 patients, including 262 who progressed to KF as defined by the initiation of dialysis or preemptive kidney transplantation over 3-year follow-up. UP analysis was performed on samples collected at baseline using capillary electrophoresis coupled to mass spectrometry. Three logistic regression models with elastic-net penalty were developed with different sets of predictors: (1) peptides alone, (2) RF including age, sex, eGFR and urinary albumin to creatinine ratio, and (3) peptides and RF. We performed 50-repeated 2-fold cross-validation to choose the 3 optimal models and measure their performances (AUC, sensitivity, and specificity). Externally independent validation was performed in a Belgian cohort of 270 patients with CKD Stages G3-G5 including 28 progressing to KF over 3-year follow-up.

**Results:** A signature of 174 peptides predicted KF risk in the first model (Figure). The independent validation of the UP signature in the Belgian cohort confirmed the prognostic potential of the peptide signature displaying a AUC of 0.928 (0.877-0.969) (sensitivity, 86%; [71%-96%] and specificity, 81%; [65%-94%]). RF alone also predicted KF risk with high precision, and the addition of peptides did not significantly improve this prediction (Figure).

**Conclusions:** We have identified a UP signature that predicts KF risk with high precision, but did not significantly ameliorate the prediction obtained by a combination of age, sex, eGFR and albuminuria.

**Funding:** Government Support - Non-U.S.

PO2361

Plasma Biomarkers of Incident CKD in Individuals Without Incident CKD

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**Background:** Earlier prediction of CKD may facilitate risk factor mitigation prior to advanced disease. Albuminuria and reduced GFR are relatively insensitive markers of early CKD. We examined the association of several novel plasma biomarkers with incident CKD.

**Methods:** We used a case cohort design in participants without diabetes in the SPRINT trial participants with baseline eGFR < 60ml/min/1.73m2, we measured a panel of 10 solutes in serum and urine, that were previously identified as markers of tubular secretion. We created a standardized composite secretory score using the urinary to plasma ratios of all 10 biomarkers. We evaluated associations of this composite score with annual % eGFR decline and progression of CKD (>30% loss of eGFR) using multivariable linear regression and Cox regression models, respectively.

**Results:** Mean participant age at baseline was 73 years, 41% were female, and 24% identified as Black. The mean eGFR varied by secretion score quartile: from 39 ml/min/1.73m2 in the lowest quartile to 51 ml/min/1.73m2 in the highest quartile. In multivariable adjusted analyses, eGFR declined faster for participants in the lower two quartiles of secretory score compared with participants in the higher two quartiles (Figure). There was no significant association between secretion score and randomized treatment assignment for the outcome of eGFR decline. In unadjusted models, each 1-SD higher secretion score was associated with a lower risk of CKD progression (HR 0.49; 95% CI, 0.35, 0.70), but this association was attenuated by multivariable adjustment (HR 0.75; 95% CI, 0.53, 1.07).

**Conclusions:** Impaired secretory function as measured by a panel of endogenous markers is associated with faster decline in eGFR among persons with CKD.

**Funding:** NIDDK Support

**Figure:** Multiple adjusted association of secretory score quartile with % eGFR decline

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

723
PO2363

The Use of Plasma Biomarker-Derived Clusters for Clinicopathologic Phenotyping: Results from the Boston Kidney Biopsy Cohort

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Background: Protein biomarkers may provide non-invasive insight into kidney disease pathology. Prior studies have not evaluated whether unsupervised clustering analyses of multiple plasma protein biomarkers may identify phenotypically distinct kidney diseases.

Methods: We performed unsupervised hierarchical clustering on 225 plasma biomarkers measured in 541 individuals enrolled into the Boston Kidney Biopsy Cohort, a prospective cohort study of individuals undergoing clinically indicated native kidney biopsy with adjudicated clinicopathologic diagnoses and semiquantitative scores of histopathology. Chi-square tests compared differences in proportions of clinicopathologic diagnoses by cluster membership. We examined contributions of biomarkers to each cluster and explored cluster-specific pathways using principal component analysis and pathway enrichment analysis, respectively.

Results: The biomarker-derived clusters partitioned subjects into 3 groups. The mean eGFR was 71.4±29.2, 72.5±34.3, and 39.3±31.3 mL/min/1.73m² in Cluster 1, 2, and 3, respectively. Compared to Cluster 1, individuals in Cluster 3 were more likely to have tubulointerstitial disease (p<0.001) and diabetic nephropathy (p<0.001), (Figure 1). The top-contributing biomarker in Cluster 1 was AXIN, a negative regulator of the Wnt signaling pathway. The top-contributing biomarker in Cluster 2 and 3 was Placental Growth Factor, a member of the VEGF family. The top ranked pathways were tumor-necrosis factor-related signaling and interleukin and cytokine signaling in Cluster 1, 2, and 3, respectively.

Conclusions: Clusters of plasma biomarkers may identify individuals with distinct forms of CKD, which may uncover relevant pathways and biomarker candidates for clinicopathologic phenotyping of kidney diseases.

Funding: NIDDK Support

PO2364

DAPA-CKD: A Regional Analysis of Kidney and Cardiovascular Outcomes

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Background: The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria, with and without type 2 diabetes. We aimed to determine whether the effects of dapagliflozin varied by pre-specified geographic region.

Methods: We randomized 4304 adults with baseline estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to dapagliflozin 10mg or placebo once daily; median follow-up was 2.4 years. We compared baseline data, primary and secondary outcomes, and safety of the 4 regions (Asia, Northern America, Latin America, Europe).

Results: Compared to other regions, participants from Asia had lower body mass index, less frequent use of diuretics and better blood pressure control. The figure displays the primary and secondary outcomes by region and treatment assignment. Dapagliflozin consistently reduced the risk of the primary composite endpoint (eGFR decline ≥50%, end-stage kidney disease, or kidney or CV death) across the 4 regions by 30 to 49%, with no significant heterogeneity (p=0.77). Similarly, there was no evidence of differences in secondary outcomes across regions. Serious adverse events in the dapagliflozin and placebo groups were similar across the 4 regions.

Conclusions: Despite differences in patient characteristics, the beneficial effects of dapagliflozin on secondary and CV endpoints in patients with CKD and albuminuria were similar across pre-specified geographic regions.

Funding: Commercial Support - AstraZeneca
Effects of Dapagliflozin in Patients with CKD and Albuminuria, with and Without Diabetes, by Use and Non-Use of Cardiovascular Medications: DAPA-CKD Trial

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Background: The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to determine whether baseline CV medications modified dapagliflozin treatment effect.

Methods: We randomized 4304 adults with baseline eGFR 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to either dapagliflozin 10 mg or placebo once daily. The primary endpoint was a composite of a ≥50% estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, and kidney or CV death. Here we categorized patients according to baseline CV medication use.

Results: Patients were required by protocol to receive a stable dose of a renin-angiotensin system inhibitor. The figure shows the effect of dapagliflozin compared with placebo, according to the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (97.0%), calcium channel blockers (50.7%), beta-blockers (39.0%), diuretics (43.7%), antithrombotic (47.4%) and lipid-lowering (69.4%) agents. The benefit of dapagliflozin was consistent across all background treatment subgroups, and findings were similar for pre-specified secondary outcomes (composite kidney endpoint, composite CV endpoint, and all-cause mortality).

Conclusions: The beneficial effects of dapagliflozin on kidney and CV endpoints in patients with CKD and albuminuria were evident among patients treated and not treated with a variety of CV medications.

Funding: Commercial Support - AstraZeneca

Efficacy and Safety of Roxadustat for the Treatment of CKD Anemia in Patients Enrolled in the United States as Compared with the Global Cohort

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Background: Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor increases hemoglobin (Hb) in non-dialysis (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Because of different clinical practices and demographic factors, it is important to evaluate efficacy and safety by region.

Methods: In a post hoc analysis of data from 3 phase 3 studies of Roxadustat vs. placebo in NDD, and 3 phase 3 studies of Roxadustat vs. epoetin alfa in DD-CKD, US patients were compared to the global cohort. Mean change from baseline in Hb averaged over weeks 28–52 regardless of rescue therapy and treatment emergent adverse events with occurrence in ≥5% of patients were assessed.

Results: Of the patients enrolled in the NDD and DD trials, 23.2% and 45.4% were enrolled in the US, respectively. Compared with global patients, US patients were older, had a higher BMI, and more frequently had type 1 or 2 diabetes mellitus and cardiovascular/chronobemobolies diseases (Table). US DD patients had a higher mean baseline Hb (SD) (10.16 g/dL [0.92]) compared with the global cohort (9.65 [1.30]). Efficacy was similar between US and global patients; least square mean (LSM) differences in NDD patients were 1.61 g/dL (95% CI: 1.48, 1.74) vs. 1.72 (95% CI:1.65, 1.79) (both p<0.0001) comparing roxadustat to placebo. LSM differences in DD patients were 0.33 (95% CI: 0.24, 0.42) vs. 0.26 (95% CI: 0.20, 0.33) (both p<0.0001) comparing roxadustat to epoetin alfa. Safety was comparable between treatment arms in US and global patients.

Conclusions: Patients enrolled in the US were older and more likely to have comorbidities in both the NDD and DD trials, Roxadustat efficacy and safety in the US were similar to global patients.

Funding: Commercial Support - FibroGen, Inc., Astellas, AstraZeneca

Quêtelet (Body Mass) Index and Effects of Dapagliflozin in CKD

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Background: The DAPA-CKD trial (NCT03036150) demonstrated a reduction of the risk of kidney and cardiovascular (CV) events with dapagliflozin in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to assess the effects of the SGLT2 inhibitor dapagliflozin in patients stratified by Quêtelet (body mass) index (BMI).
PO2368

Correlates and Consequences of an Acute Decline in Estimated Glomerular Filtration Rate in Response to the SGLT-2 Inhibitor Dapagliflozin

Hido J. Heerspank,1,2 Niels Jong,1 Glenn M. Chertow,1 Anna Maria Langkilde,4 John McMurray,5 Ricardo Correa-Rotter,4 Peter Rossing,4 David Sjostrom,4 Bergur V. Stefansson,4 Robert D. Toto,4 Tom Greene,10 David C. Wheeler,11 University of Groningen, University Medical Center Groningen, Groningen, Netherlands; 1The George Institute for Global Health, Southwestern Medical Center, Dallas, TX; 10University of Utah Health, Salt Lake City, UT; 11University College London, London, United Kingdom; 6The National Medical Science and Nutrition Institute Hiddo Dapagliflozin: Correlates and Consequences of an Acute Decline in Estimated Glomerular Filtration Rate in Response to the SGLT-2 Inhibitor Dapagliflozin

Methods: In DAPA-CKD, 4304 participants with urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g and eGFR 25–75 mL/min/1.73m2 were randomized to dapagliflozin 10 mg or placebo once daily, added to standard care, and followed for median 2.4 years. We categorized decline in eGFR from baseline to Week 2 in percentages (≥10% decline; between 0 and 10% decline; and no decline) and absolute changes (<3 mL/min/1.73m2; between 0 and 3 mL/min/1.73m2; and no decline).

Results: A total of 4157 patients (96.6% of full cohort) had eGFR data available at baseline and Week 2. In the dapagliflozin and placebo groups, 1026 (49.4%) and 494 (23.7%) experienced an acute decline in eGFR of ≥10%, respectively. The odds ratio for a decline in eGFR of ≥10% with dapagliflozin compared with placebo was 3.2 (95%CI 2.8–3.6; p<0.001). The odds ratio for an acute eGFR decline of ≥10% was consistent across patient subgroups defined by baseline sex, eGFR, UACR, diabetes status, blood pressure, body mass index, or cardiovascular disease history. The only exception was that white participants and participants age 65 years were more likely to experience an acute eGFR decline of ≥10% following dapagliflozin initiation relative to placebo (interaction p=0.025 for both). Rates of serious adverse events and adverse events of special interest in those treated with dapagliflozin were unrelated to the degree of acute eGFR decline.

Funding: Commercial Support - AstraZeneca

PO2370

Patiromer Enables Sustained RAAS Inhibitor Therapy over 52 Weeks: A Post Hoc Analysis of 246 Patients Who Completed the AMETHYST-DN Study

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Background: Hyperkalaemia (HK) is a common electrolyte abnormality in CKD patients (pts) with type 2 diabetes mellitus (T2DM) and leads to underutilization of RAAS inhibitors (RAASi). KDIGO guidelines recommend RAASi dose should be reduced or discontinued only as a last resort in HK pts after measures to control serum potassium (sK) have failed. Patiromer (PAT) is a non-absorbed, sodium-free, K binder documented to reduce sK in pts with HK, and consequently enables sustained RAASi therapy. This post-hoc analysis of AMETHYST-DN analyzed in-depth the ability of PAT to maintain RAASi in a large cohort of pts with diabetic kidney disease (DKD) and HK who completed 1 year of treatment with PAT.

Methods: AMETHYST-DN was a multicenter, open-label trial of PAT in adult pts on stable RAASi therapy with eGFR 15–<60 mL/min/1.73m2 with proteinuria ≥2 g/day. Pts were randomized to PAT or placebo (PL) plus RAASi. Treatment was 60% at baseline declining to 43% at 12-month follow-up in the SKS cohort. Trend analysis showed a significant difference in the rate of change in proteinuria at 12 months in AMETHYST-DN vs SKS pts (~31 mg/g vs ~9 mg/g, p=0.023).

Conclusions: PAT enabled sustained RAASi use in 99% of pts in AMETHYST-DN, compared to 43% in a matched SKS cohort over 12 months. AMETHYST-DN pts had significantly reduced proteinuria at follow-up compared to SKS CKD pts, possibly due to continuation of RAASi enabled by PAT. No significant changes in eGFR were observed in either group.

Funding: Commercial Support - Vifor Pharma

Table 1. Differences in baseline and global cohorts in demographic and disease characteristics

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<th>Parameters</th>
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<th>Global (n=3564)</th>
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<td>Male (%)</td>
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</tr>
<tr>
<td>Diabetes (%)</td>
<td>93.9</td>
<td>93.9</td>
<td>0.25</td>
</tr>
<tr>
<td>CKD stage (%)</td>
<td>89.4</td>
<td>89.4</td>
<td>0.25</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140.0 (17.0)</td>
<td>140.0 (17.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84.0 (9.8)</td>
<td>84.0 (9.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>45.3 (20.9)</td>
<td>45.3 (20.9)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Table 2. Outcomes in the matched sample of patients from SKS and AMETHYST-DN

<table>
<thead>
<tr>
<th>Serum potassium (mg/dL)</th>
<th>SKS (n=2568)</th>
<th>AMETHYST-DN (n=719)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.2 (0.5)</td>
<td>5.2 (0.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Follow-up</td>
<td>4.6 (0.5)</td>
<td>4.6 (0.5)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 3. Adverse events of special interest

<table>
<thead>
<tr>
<th>Event</th>
<th>SKS (n=2568)</th>
<th>AMETHYST-DN (n=719)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalaemia</td>
<td>10 (0.4%)</td>
<td>7 (0.9%)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Affiliations: 1University of Miami School of Medicine, Miami, FL; 2Vifor Pharma Group, Redwood City, CA
for clinical reasons (AEs, 12; low sK, 5; death, 4; deterioration of renal function, 4; high sK), whereas 22 had reasons related to investigator/patient factors (consent withdrawal, 12; noncompliance, 7; investigator decision, 1; other, 2). During the LTMP, 1 AE was reported for 158/246 pts.

Conclusions: This analysis of AMETHYST-DN demonstrates that the vast majority of patients undergoing prednisolone withdrawal followed the protocol. Of the 22 patients who completed the LTMP of the study, 4 CE were unable to sustain their RAASi dose over an extended 44 weeks without discontinuation or downtitration of RAASi therapy. Only 2 pts withdrew early from the LTMP due to recurrent HK.

Funding: Commercial Support - Vifor Pharma

PO2371
Predict Hyperkalemia in Advanced CKD Patients Using Machine Learning Algorithms

Hsin-Hsiung Chang,1 Chia-Lin Wu,1 Paochien Hospital, Pingtung, Taiwan; 2Changhua Christian Hospital, Changhua, Taiwan.

Background: Hyperkalemia is a common and fatal problem in advanced chronic kidney disease patients. The incidence rate was about 40-50%. It may cause muscle weakness, paralysis, and even cardiac arrhythmia. Our goal is to develop machine learning models to predict hyperkalemia in advanced chronic kidney disease patients, which could help physicians make clinical decisions.

Methods: We collected clinical data for advanced CKD (CKD stage 4 and 5, eGFR < 30 ml/min/1.73m²) patients receiving Output Patient Care in one medical center in Taiwan from January 2010 to December 2019, 1,965 patients were included. Four machine learning models (multilayer perceptron [MLP], logistic regression with regularization, XGBoost, and random forest [RF]) were used to estimate serum potassium concentration 3 months later. 2 Nephrologists participated in human-machine competition. Area under the receiver operating characteristic curves (AUCs), sensitivity, specificity, positive (PPV) and negative (NPV) predicted values, and accuracy were used to evaluate the performance of machine learning models with that of these physicians.

Results: In a test set including 2,074 records, the AUC of machine learning models was 0.82 (95%CI: 0.78-0.86), whereas 22 had reasons related to investigator/patient factors (consent withdrawal, 12; noncompliance, 7; investigator decision, 1; other, 2). During the LTMP, 1 AE was reported for 158/246 pts.

Conclusions: Machine learning models may help physicians make clinical decisions in advanced CKD patients who suffer from hyperkalemia in outpatient department care and possibly reduce cardiac arrhythmia.

PO2372
Association Between Dietary Potassium Intake and Abdominal Aortic Calcification in US Adults

Yuping Xie,1 Matthew K. Abramowitz,2 Wei Chen,*1 Children’s Hospital at Montefiore, Bronx, NY; 1Albert Einstein College of Medicine, Bronx, NY.

Background: In ApoE-deficient mice, low dietary potassium intake promoted vascular calcification and high dietary potassium intake attenuated vascular calcification. We hypothesized high dietary potassium intake was associated with lower abdominal aortic calcification (AAC) among adults in the US.

Methods: Cross-sectional analyses were performed on 2,535 participants from the National Health and Nutrition Examination Survey 2013-2014. Dietary potassium intake was obtained from two 24-h recall interviews and were categorized into quartiles (Q1: 0.3-1.9, Q2: 2.0-2.4, Q3: 2.5-3.1 and Q4: 3.2-6.8 g/day). AAC was measured using dual-energy X-ray absorptiometry in adults over 40 years old and quantified using the Kaupilia score system. AAC scores were categorized into: no AAC (AAC=0, reference group), mild/moderate (AAC=0-6.6) and severe AAC (AAC=6). Multinomial logistic regression was used to study the association between AAC and dietary potassium intake. Model was adjusted for demographics, hypertension, diabetes, smoking, eGFR, albuminuria, BMI, energy intake and physical activity.

Results: In the entire cohort, mean dietary potassium intake was 2.4±1.1 g/day; 21% had mild/moderate AAC and 9.8% had severe AAC. Dietary potassium intake was not associated with mild/moderate AAC (table). For severe AAC, dietary potassium intake was only associated with AAC when comparing dietary potassium in Q2 with Q1; Q2 was associated with lower odds of having severe AAC (OR 0.65 [95% CI: 0.46-0.92], p=0.02). This association remained significant in the fully adjusted model (OR 0.50 (95% CI: 0.29-0.86), p=0.02). This association remained significant in the fully adjusted model (OR 0.50 (95% CI: 0.29-0.86), p=0.02).

Conclusions: Higher dietary potassium intake was associated with lower AAC, but the association is only significant when comparing dietary potassium intake in Q2 with Q1. This nonlinear relationship between dietary potassium intake and AAC was obtained from two 24-h recall interviews and were categorized into quartiles (Q1:0.3-1.9, Q2: 2.0-2.4, Q3: 2.5-3.1 and Q4: 3.2-6.8 g/day). AAC was measured using dual-energy X-ray absorptiometry in adults over 40 years old and quantified using the Kaupilia score system. AAC scores were categorized into: no AAC (AAC=0, reference group), mild/moderate (AAC=0-6.6) and severe AAC (AAC=6).

PO2373
Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria

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Background: Early safety signals suggested potential nephrotoxicity with rosuvastatin, and the US FDA recommends a maximum dose of 10 mg for patients with severe CKD. Whether these recommendations are followed and whether rosuvastatin use is associated with nephrotoxicity in real-world practice is uncertain.

Methods: Using data from OptumLabs® Data Warehouse, a database that contains de-identified claims and electronic health record data, we identified adult patients who initiated rosuvastatin (N=155416) or atorvastatin (N=793513) in 44 health systems (“cohorts”) between 2011-2019, were free of ESKD, and did not have history of hematuria or proteinuria at the time of prescription. The outcomes were hematuria (dipstick hematuria+) or presence of ≥3 red blood cells in urine microscopy) and proteinuria (dipstick proteinuria+ or urine albumin-to-creatinine ratio>100 mg/g).

Results: Overall, 2.6% and 0.8% of patients developed hematuria and proteinuria during a median follow-up of 2.6 years. Compared with atorvastatin, rosuvastatin was associated with an increased risk of hematuria (HR 1.07 [95% CI 1.03-1.11]) and proteinuria (1.18 [1.11-1.26]). Among those with eGFR<30 ml/min/1.73 m², rosuvastatin use was associated with greater risk of hematuria (1.78 [1.25-2.54]) and proteinuria (1.80 [1.15-2.83]) (Figure). Patients with eGFR<30 ml/min/1.73 m² frequently were prescribed a higher rosuvastatin dose than the maximum recommended dose of 10 mg; 30.5% received 20 mg while 14.4% received 40 mg.

Conclusions: Among patients with eGFR<30 ml/min/1.73 m², the use of higher-than-recommended dose rosuvastatin was common, and rosuvastatin was associated with an almost 2-fold increased risk of hematuria and proteinuria.

Funding: NIDDK Support

PO2374
Hydrophilic vs. Lipophilic Statin Treatments in Patients with CKD After Acute Myocardial Infarction: A Propensity Score-Matched Comparison

Hyung Hwan Kim,1 Soo-Young Yoon,1 Dae Kyu Kim,1 Shinyeong Kang,3 Jin sug Kim,1 Kyung hwan Jeong,2 Hyeon Seok Kwang.1 Kyung Hee University Medical Center, Seoul, Republic of Korea.

Background: Effect of statin treatment is critical to prevent major adverse cardiac and cerebrovascular events (MACES) after acute myocardial infarction (AMI). Earlier studies demonstrated that the lipophilicity of statin did not affect prognosis in AMI patients without renal dysfunction. However, the effect of statin lipophilicity was not investigated in chronic kidney disease (CKD) patients.

Methods: We enrolled total 2,620 AMI patients with chronic kidney disease (CKD) from Korea Acute myocardial infarction Registry between November 2011 and December 2015. CKD was defined as an eGFR < 60ml/min/1.73 m². Patients were divided into two groups based; hydrophilic (n = 663), lipophilic (n = 1399) statin treatment. The primary endpoint was a combination of 2-year major MACES after AMI occurrence. Subsequently, a binary variable score matched analysis was performed.

Results: The lowest cumulative event rate of MACE (HR 0.71 [95% CI 0.55-0.91], p=0.007), all-cause mortality (HR 0.68 [95% CI 0.50-0.94], p=0.018), recurrent MI (HR 0.42 [95% CI 0.23-0.76], p=0.005) was observed in patients treated with hydrophilic statins. Sensitivity -matched and CDRs were performed.

Conclusions: Machine learning models may help physicians make clinical decisions in advanced CKD patients who suffer from hyperkalemia in outpatient department care and possibly reduce cardiac arrhythmia.
PO2375

The Effect of Fibrates on Kidney Function and CKD Progression: A Systematic Review and Meta-Analysis of Randomised Studies

Alexandros Hadjivassiliou,1 Andreas Kousios,2,3 Panayiotis Kouis,3 Andric G. Panayiotou.4,5 Technologiko Panepistemio Kyprou, Limassol, Cyprus; 2Hammersmith Hospital, London, United Kingdom; 3Imperial College London, London, United Kingdom

Background: Fibrates have proven efficacy in cardiovascular risk reduction and are commonly used, in addition to statins, to control hyperglycemia. Their use is often limited due to reduction in glomerular filtration rate at treatment initiation. However, recent studies suggest benefit change in kidney function and improvement of proteinuria; an established early marker of microvascular disease and kidney disease progression. We summarize the evidence from existing trials and provide summary effects of fibrates, alone or in combination, on kidney disease progression and proteinuria.

Methods: Systematic review and Meta-analysis of randomised controlled trials (PROSPERO CRD2020187874).

Results: Out of 12243 potentially eligible studies, 29 were included in qualitative and quantitative analysis, with a total of 20176 patients. Mean creatinine increased by 1.05 (95% CI:0.63 to 1.46) units in patients receiving fibrates vs comparator, and this was similar in all other subgroups. eGFR showed a bigger decrease in the fibrates arm (SMR -1.99; 95% CI:3.49-0.48) when all studies were pooled together. Notably short-term serum creatinine and eGFR changes remained constant in the long-term. Pool estimates show that fibrates improve albuminuria progression, RR 0.86; 95% CI:0.76 to 0.98; albuminuria regression, RR 1.19; 95% CI:1.08 to 1.310). Two studies showed reduction in progression to ESKD, albeit without statistical significance.

Conclusions: Fibrates improve albuminuria in patients with and without diabetes when used to treat hyperlipidemia. The modest creatinine increase should not be a limiting factor for fibrate initiation in people with preserved renal function or mild CKD. The long-term effects on kidney disease progression warrant further study.

PO2376

The Effect of Atrasentan on Kidney and Heart Failure Outcomes by Baseline Albuminuria and Kidney Function: A Post Hoc Analysis of the SONAR Trial

Simone W. Winger,1 Ron T. Gansevoort,1 George L. Bakris,2 Ricardo Cortea-Rotter,3 Fan Fan Hou,4 Donald E. Kohan,5 Hirofumi Kohan,5 John McMurray,6 Vladko Perkovic,7 Sheldon W. Tobe,1 Hans-Henrik Parving,10,11 Dick de Zeeuw,1 Hiddo J. Heerspink,1 1Universitat Medizcn Centrum Groningen, Groningen, Netherlands; 2The University of Chicago Medicine, Chicago, IL; 3Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; 4Robarts Research Institute, University of Western Ontario, London, ON, Canada; 5University of Utah Health, Salt Lake City, UT; 6University of Glasgow, Glasgow, United Kingdom; 7The George Institute for Global Health, Newtown, NSW, Australia; 8Okayama Daigaku, Okayama, Japan; 9Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 10Rigshospitalet, København, Denmark; 11Aarhus Universitet, Aarhus, Denmark

Background: Atrasentan reduces kidney failure risk, but increases risk of edema and possibly heart failure in patients with diabetic kidney disease. Patients with advanced chronic kidney disease (CKD) may obtain greater absolute renal benefit from atrasentan but may be at higher risk of renal retention due to impaired renal excretory capacity. We assessed effects of atrasentan on kidney and heart failure events according to baseline eGFR and albumin:creatinine ratio (UACR) in a post-hoc analysis of the SONAR trial.

Methods: The effect of atrasentan versus placebo in 3668 patients with type 2 diabetes and CKD with elevated UACR was examined in SONAR. We used Cox regression to study effects on the primary kidney outcome (doubling of serum creatinine, end-stage kidney disease or renal death) and heart failure hospitalization across subgroups of eGFR (<30, ≥30-45, ≥45 ml/min/1.73 m2) and UACR (<1000, ≥1000-3000, ≥3000 mg/g).

Results: Atrasentan reduced the relative risk of the primary kidney subgroup (HR 0.71, 95%CI 0.58-0.88) consistently across subgroups of baseline eGFR and UACR (table). Patients in the highest UACR and lowest eGFR subgroups showed the largest absolute benefit (all P-interaction <0.01). The relative (HR 1.39, 95%CI 0.97-1.99) and absolute risk of heart failure hospitalization was consistent across eGFR and UACR subgroups (all P-interaction >0.09).

Conclusions: Atrasentan reduced the relative risk of the primary kidney outcome consistently across baseline eGFR and eGFR subgroups. The absolute risk reduction was small in the 2 lowest eGFR subgroups but at highest baseline eGFR (HR 0.71, 95%CI 0.58-0.88) consistently across subgroups of baseline eGFR and UACR (table). Patients in the highest UACR and lowest eGFR subgroups showed the largest absolute benefit (all P-interaction <0.01). The relative (HR 1.39, 95%CI 0.97-1.99) and absolute risk of heart failure hospitalization was consistent across eGFR or UACR subgroups (all P-interaction >0.09).

PO2377

The Comparative Effectiveness and Safety of Rivaroxaban and Warfarin Initiation in Adults with Atrial Fibrillation (AF) by eGFR Category

Tobe,1 Lesley A. Inker,2 Mara McAdams-DeMarco,3 Morgan Grams,4 Jung-Im Shim,1 Johns Hopkins University, Baltimore, MD; 2Geisinger Health, Danville, PA; Tsufs Medical Center, Boston, MA; Johns Hopkins Medicine, Baltimore, MD

Background: The risk-benefit ratio of rivaroxaban, a commonly prescribed direct oral anticoagulant, relative to warfarin in patients with atrial fibrillation (AF) and CKD is uncertain.

Methods: We conducted an international multicenter cohort study (2011-2018) using retrospective data from 5 jurisdictions across Australia (530 participants of the 45 and Up Study [among 267153 recruited in 2006-09] with data, accessed via SURE, linked to hospital/laboratory data [by CHReL] and the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data provided by Services Australia) and Canada (55038 patients in AB,BC,MB,ON; record linkage of provincial administrative/laboratory data). We created a quality score matched adults with a new prescription of rivaroxaban or warfarin, who had AF and a recorded eGFR grouped ase0.60-59.00, ~30-59ml/min/1.73m2. Chronic dialysis or kidney transplant recipients were excluded. We assessed 2 composite outcomes within 1 year of initiating either therapy: ischemic (all-cause death, ischemic stroke, or transient ischemic attack), and bleeding events (intracranial, gastrointestinal or other). We used Cox regression to estimate the hazard ratios of each outcome across eGFR categories and summarized centre data in random effects meta-analysis.

Results: Of the 55038 matched rivaroxaban and warfarin users, 4733(8.5%) experienced an ischemic event and 1145(2%) a bleeding event. As compared to warfarin initiation, rivaroxaban initiation was associated with lower or similar hazard for the ischemic outcome (HR 0.95 CI: 0.72-0.66, 0.78-0.57-0.87 and 0.78-0.50-0.99, for eGFR ≥60, 45-59, 30-44 and <30ml/min/1.73m2 respectively. Rivaroxaban initiation was also associated with lower or similar hazard for the bleeding outcome (0.70-0.49-1.00), 0.50-0.78-1.29, 0.85-0.64-1.12, 0.61-0.35-0.51). We observed no evidence of heterogeneity across centers except for eGFR 45-59ml/min/1.73m2 for the ischemic outcome(=77%) and ≥60ml/min/1.73m2 for the bleeding outcome(=62%).

Conclusions: Compared to warfarin, rivaroxaban initiation was associated with lower or similar risk of both ischemic and bleeding outcomes independent of eGFR. Sufficiently powered randomized trials are needed to confirm findings from this large international cohort.

Funding: Government Support - Non-U.S.
PO2379

Association of Long-Term Aspirin Use with Progression of Kidney Disease

Jun Ting Lu,1 Fridjof Thomas,1 Keichi Sumida,1 Waleed Hassan,1 Csaba P. Kovetsy,2,3 The University of Tennessee Health Science Center, Memphis, TN; 2VA Memphis Medical Center, Memphis, TN.

**Background:** Aspirin (ASA) has been used to control inflammation for over a century. Recently, chronic microinflammation was detected to be a major contributor to the progression of chronic diseases such as cancer and chronic kidney disease (CKD). However, it is unclear if long-term use of ASA could lower mortality and slow renal deterioration in patients with CKD.

**Methods:** We identified 860 US Veterans with non-dialysis dependent CKD followed at a single medical center between October 2014 to September 2015. Associations between long-term ASA use (at least 90 days) with mortality, and with a combined renal outcome (dialysis or eGFR dropping 40% from baseline) were examined in multivariable adjusted Cox proportional hazards models. Besides the crude model (model 1), we adjusted for demographics, BMI, smoking status, blood pressure (model 2), for comorbidities (Model3), and for anthypertensive medications, NSAIDs, steroids, baseline eGFR, medication adherence rate, and proteinuria (Model 4).

**Results:** The mean age (SD) of ASA users vs. non-users was 68.1 (9.9) vs. 64.2 (13.1) years, and the mean eGFR (SD) was 36.9 (0.7) ml/min/1.73m² vs. 43.7 (2.0). Over a 4.6-year median follow-up period, 37% of patients reached the combined renal endpoint (event rate: 102.8/1000 patient-years) and 372 (43%) patients died. ASA users demonstrated a lower risk of the renal outcome ( Hazard Ratio [HR] 0.53 [95%CI: 0.41, 0.74], p<0.001) and a lower mortality rate (HR 0.40 [95%CI: 0.26, 0.64], p<0.001) in the fully adjusted model [Figure].

**Conclusions:** CKD patients receiving ASA for 90 days or longer had slower deterioration of kidney function and lower mortality. Further clinical trials are required to investigate the benefits of ASA in this population.

![Association between Aspirin use and Outcomes](image)

**Data**

- **ASA Users vs. Non-users**: Age: 68.1 (9.9) vs. 64.2 (13.1) years
- **Mean eGFR**: 36.9 (0.7) ml/min/1.73m² vs. 43.7 (2.0)
- **Combined Renal Endpoint**: Event rate: 102.8/1000 patient-years
- **Mortality Rate**: HR 0.40 [95%CI: 0.26, 0.64], p<0.001

PO2380

Treatment of Hyperuricemia and Incident CKD in Patients with Normal Kidney Function

Waleed Hassan,1 Praveen Kumar Potukuchi,1 Ankur A. Dashputre,1 Keichi Sumida,1 Fridjof Thomas,1 Elani Streja,1 Kamyar Kalantar-Zadeh,1 Csaba P. Kovetsy,1,4 The University of Tennessee Health Science Center College of Medicine, Memphis, TN; 2The University of Tennessee Health Science Center, Memphis, TN; 3University of California Irvine, Irvine, CA; 4VA Memphis Medical Center, Memphis, TN.

**Background:** Hyperuricemia is associated with incident chronic kidney disease (CKD) independent of established metabolic risk factors. Treatment of hyperuricemia with uric-acid lowering therapy (ULT) was not beneficial in clinical trials of patients with CKD, but the effects of ULT on incident CKD in patients with no pre-existing CKD is unclear.

**Methods:** We identified a national cohort of US Veterans with normal kidney function (eGFR >60 ml/min/1.73m² and no proteinuria) and serum uric acid measurement. We examined the association of incident new ULT use (vs. no ULT), with the incidence of CKD (defined as 2 measurements of eGFR <60 ml/min/1.73m² or UACR >30 mg/gm at least 90 days apart), using time dependent Cox models adjusted for baseline demographic characteristics, comorbid conditions, and time dependent eGFR and serum uric acid concentration.

**Results:** We identified 1,152,040 patients with a serum uric acid measurement, of whom 111,508 (10%) patients received de novo ULT during 2006-2019. The overall mean (SD) age was 59 ±13 years, 94% were male, 76% were white, and the mean (SD) eGFR was 84 (17) ml/min/1.73m² at the cohort entry. There were 308,311 cases of incident CKD (event rate, 40.4/1000 PY; 95%CI, 40.3-41.6) over a median follow-up of 6.1 years. ULT was associated with higher risk of incident CKD in both crude models (hazard ratio, 2.50 [95%CI: 2.25-2.76]) and after multivariable adjustments (HR, 1.45; 95%CI, 1.44-1.47) [table].

**Conclusions:** Although hyperuricemia is independently associated with risk of CKD, treatment of hyperuricemia with ULT was not associated with lower risk of incident CKD in patients with baseline normal kidney function and no proteinuria in a large national cohort.

**Funding:** Veterans Affairs Support

![Data](image)

**Table**

<table>
<thead>
<tr>
<th>ULT</th>
<th>No ULT</th>
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</thead>
<tbody>
<tr>
<td>Incident CKD (rate/1000 PY)</td>
<td>40.4 (95%CI: 40.3-41.6)</td>
</tr>
<tr>
<td>Crude Hazard Ratio [95%CI]</td>
<td>2.50 [2.25-2.76]</td>
</tr>
<tr>
<td>Adjusted Hazard Ratio [95%CI]</td>
<td>1.45 [1.44-1.47]</td>
</tr>
</tbody>
</table>

PO2381

Trial Design of FRONTIER: Ferric Citrate for the Prevention of Renal Failure in Adults with Advanced CKD

Geoffrey A. Block,2 Martha Block,1 Stephanie Brillhart,1 Mary O. Dittrich,1 Glenn M. Chertow,2 Navdeep Tangri,3 ‘US Renal Care, Inc, Plano, TX; 3Stanford University School of Medicine, Stanford, CA; 4University of Manitoba, Winnipeg, MB, Canada.

**Background:** There are no approved therapies to delay progression to RRT or improve survival specifically in patients with advanced CKD regardless of etiology. A pilot open-label randomized trial in 200 patients with estimated GFR < 20 ml/min/1.73m² demonstrated statistically significant reduction in the risk of the composite endpoint of death, dialysis or transplantation in patients randomized to fixed dose ferric citrate coordination complex (FCCC) as compared to standard of care (SOC). The current trial is designed to overcome the limitations of this open-label RCT by using a pragmatic, placebo-controlled, randomized trial design.

**Methods:** FRONTIER will enroll 1000 patients with estimated GFR < 20 ml/min/1.73m² who will be randomized 1:1 to either fixed dose FCCC (2 tablets/meal) or matching placebo. Enrollment will not be based on serum concentrations reflecting iron sufficiency or phosphate. Subjects will be followed for 18 months using a pragmatic schedule based solely on SOC visits. No additional trial specific visits or laboratory tests will be required. The primary objective is to determine the effect of FCCC on the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality compared to placebo. The secondary objective is to evaluate the impact of FCCC on all-cause hospitalization and the individual components of the primary endpoint.

**Results:** FRONTIER is a collaboration between Industry (Akebia Therapeutics is providing study medication and funding), community nephrologists (planned for 42 sites in the US) and academia. An executive steering committee has designed the clinical trial protocol and US Renal Care, Inc will be acting as the Sponsor-Investigator.

**Conclusions:** Based on supportive pilot data, FRONTIER will utilize a novel trial design incorporating a pragmatic approach while maintaining a randomized, placebo-control arm and generating real-world evidence to determine the effects of FCCC on clinically meaningful patient outcomes (time to dialysis or all-cause mortality).

**Funding:** Commercial Support - Akebia Therapeutics

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

729
PO2382
Effect of Oral Sodium Bicarbonate on Biomarkers of Bone Turnover in CKD: A Secondary Analysis of the BASE Pilot Trial
Kalani L. Raphael,1 Ronit Katz,2 Tamara Isakov,2 Stuart M. Sprague,3 Myles Wolff,2 Dominic S. Raj,2 Andrew N. Hoofnagle,2 Brett Larive,3 Cynthia A. Kendrick,3 Jennifer J. Gassman,1 Linda F. Fried,3 Alfred K. Cheung,2 Joachim H. Ix,2 Oregon Health & Science University School of Medicine, Portland, OR; 3Portland VA Medical Center, Portland, OR; 1University of Washington, Seattle, WA; 2Northwestern University, Evanston, IL; 7NorthShore University HealthSystem, Evanston, IL; 8Duke University, Durham, NC; 4Georgia Washington University Medical Faculty Associates, Washington, DC; 5University of Utah Health, Salt Lake City, UT; 9University of California San Diego, La Jolla, CA; 10Cleveland Clinic, Cleveland, OH; 11VA Pittsburgh Healthcare System, Pittsburgh, PA

Background: CKD clinical practice guidelines recommend treatment with alkali to mitigate adverse effects of metabolic acidosis on several organ systems, including bone. The effect of alkali supplementation on bone turnover in CKD is unclear. We performed a secondary analysis of the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial to investigate the effect of NaHCO3 on biomarkers of bone turnover.

Methods: BASE randomized 194 individuals with eGFR 20-59 ml/min/1.73m2 to receive placebo (n=52) or one of two doses of NaHCO3, (0.5 mEq/kg/d, n=52; 0.8 mEq/kg/d, n=90) for 28 weeks. We measured serum parathyroid hormone (PTH), bone-specific alkaline phosphatase (B-SAP), C-telopeptide (CTX, marker of bone resorption), and procollagen type I propeptide (PINP, marker of bone formation) levels from stored samples collected at baseline, week 12, and week 28, and compared the mean change from baseline between placebo and those treated with NaHCO3 using linear mixed models.

Results: 168 of 194 participants (86%) submitted samples for post-hoc measurements (placebo, n=46; lower-dose, n=47; higher-dose, n=75). Baseline characteristic were age 67±12 years, female 28%, Black, 32%, Hispanic 15%, eGFR 37±10 ml/min/1.73m2, serum total CO2 24±3 mmol/L, B-SAP 12.8±5.0 g/L, CTX 0.36±0.38 mg/mL, and PINP 57±31 mg/mL. NaHCO3 treatment raised PTH and lowered B-SAP, however there was no significant difference when compared to placebo. NaHCO3 treatment had no effect on CTX or PINP (Table).

Conclusions: NaHCO3 treatment did not have consistent effects on biomarkers of bone turnover as assessed by PTH, B-SAP, CTX, or PINP, and no significant effects relative to placebo in patients with CKD.

Funding: NIDDK Support

Table 1. Change in biomarker levels over 28 weeks among treatment groups

PO2383
Can Structured, Moderate Exercise Slow Kidney Function Decline in Sedentary Elders?
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Background: In numerous observational studies, higher physical activity is associated with slower declines in kidney function; however, no large trial has evaluated whether exercise to slow kidney function decline in older adults. The Lifestyle Interventions and Independence For Elders (LIFE) was a randomized clinical trial that demonstrated that a structured, moderate intensity physical activity (PA) intervention compared to a health education (HE) control intervention reduced the incidence of major clinical outcomes among sedentary elders.

Methods: The LIFE-Kidney ancillary study evaluated whether this exercise intervention slowed kidney function decline over 2 years compared with a control arm of health education.

Funding: NIDDK Support

Table 1 Change in biomarker levels over 28 weeks among treatment groups

PO2384
Effect of Applying 6% Low-Protein Formula to Dietary Advice in Elderly CKD Patients: A Randomized Control Trial
Cheng-Hsu Chen,1 Wen-Ching Yang,3 Li-Chun Liu,1 Hui-Min Hsieh. Taichung Veterans General Hospital, Taichung, Taiwan.

Background: The majority of researchers have suggested the benefit of low-protein diet (LPD) could delay renal function progression in chronic kidney disease (CKD), but LPD increases the risk of malnutrition. The purpose of this study to determine the effectiveness of dietary advice usings 6% low protein formula (6% LPF) for elderly CKD patients.

Methods: Patient were recruited aged over 65 years old who were diagnosed stages 3-5 CKD. There were randomized to general LPD advice (control group) or LPD advice combined with low-protein formula use. The dietary advice (intervention group) for renal dieting during 3 months treatment. 6% LPF was prescribed daily, providing 400 kcal energy, 6 g of protein. The data analyzed were measured body weight (BW), body mass index (BMI), hand grip strength (HGS) in nutrition status and blood urea nitrogen (BUN), creatinine and estimated glomerular filtration rate (eGFR) in kidney function parameter.

Results: 95 patients enrolled, and 47 completed of this study was distribution to intervention group (n=24) and control group (n=23). During the study period, HGS was maintained in intervention group but decreased significantly in control group (P=0.02). However, creatinine and BMI in both group were no significant differences. BUN was significantly reduced in intervention group (p=0.003) but not control group (p=0.059). There were no differences in creatinine and eGFR between groups at baseline to 3 months. Conclusion: Compared with routine LPD prescription, which combined with supplemented 6% LPF was associated with maintained nutrition status and prevention of renal failure. Our findings suggested that 6% LPF was a complementary strategy routine LPD education protocol.

Funding: NIDDK Support

Table 1 Change in biomarker levels over 28 weeks among treatment groups

PO2385
Incident Biologic Use and Risk of ESKD in Patients with Inflammatory Bowel Disease
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Background: Inflammatory bowel disease (IBD) is associated with reduced kidney function, possibly due to chronic inflammation or the use of nephrotoxic therapies. Little is known about the effects of IBD therapy using novel biologic agents on the risk of incident end-stage kidney disease (ESKD). Methods: In a nationwide cohort of 66,602 US veterans with an eGFR ≤60 mL/min/1.73m2 from 2004-2006 who were newly diagnosed with IBD (at least 2 IBD diagnoses that were 30-365 days apart) during follow-up through 2018, we examined the association of incident biologic use (as a time-dependent exposure) with incidence of ESKD, using time-dependent Cox models adjusted for sociodemographics, comorbidities, and alcohol use, comorbidities, IBD, vital signs, and relevant medications (e.g., antihypertensives, NSaiDs, steroids, nonbiologic DMARDs).

Results: At baseline, the two groups were well balanced by age, comorbidity and physical limitations, and had comparable eGFR. The PA group had eGFR values 0.5 and 1.5 ml/min/1.73m2 higher at years 1 and 2, respectively, and the average effect across the 2 follow-up visits was significantly different (p<0.04). Those in the PA arm were also less likely to experience a ≥6.7% annual eGFR decline compared to the HA arm (Table). In the PA arm, total steps completed was strongly associated with reduced eGFR decline (p=0.001), and mediated the effect of randomization to PA compared with HE (F statistic attenuated from 4.09 to 1.84).

Conclusions: Among sedentary elders, randomization to a program of moderate exercise slowed kidney function decline over 2 years compared with a control arm of health education.

Funding: NIDDK Support

Table 1 Change in biomarker levels over 28 weeks among treatment groups

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Patients were 69±11 years old; 93% were male; 74% were African American; 30% were diabetic; and baseline eGFR was 77±16 mL/min/1.73m². Among 66,602 patients, 1,047 (1.6%) started biologic therapy, and 504 (0.8%) experienced an incident ESKD. In a sociodemographic-adjusted model, incident biologic use (vs. non-use) was associated with lower risk of incident ESKD (adjusted HRs [95%CI], 0.55 [0.29-1.49], in model 1) albeit not reaching statistical significance. This association was attenuated after further multivariable adjustment (0.98 [0.41-2.35], in model 4; Figure).

Conclusions: Biologic agent administration is not associated with higher risk of incident ESKD. Clinical trials are warranted to test whether active interventions with biologic agents are safe and effective in preventing adverse renal outcomes associated with BD.

Funding: Veterans Affairs Support

PO2387
Association of Kidney Measures with Cardiovascular Events, Kidney Outcomes, and Mortality Among Older Adults
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Background: Based on current criteria (glomerular filtration rate [GFR] <60 mL/ min/1.73m² or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), the prevalence of CKD in U.S. older adults is up to 42% among those aged 65-79 years. However, the risk implications of this CKD definition in this population are controversial. We evaluated the risk of adverse outcomes among older adults across CKD stages based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition.

Methods: This study included 2640 older adults (age ≥75 years) without diabetes enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT). We compared the risk of the primary composite SPRINT outcome, and all-cause death, across GFR and albuminuria categories based on KDIGO guidelines. To estimate GFR, we used the CKD Epidemiology Collaboration (CKD-EPI) equation and the Berlin Initiative Study (BIS1), a novel estimator of GFR in elderly persons.

Results: Mean age was 79.8 years, 37.9% were female, 17.0% of participants self-identified as non-Hispanic Black, 6.6% as Hispanic, and 74.6% as non-Hispanic White. Mean estimated GFR was 63.3 mL/min/1.73 m², and median UACR 55 mg/g. In multivariable regression analysis, there was no statistically significant difference in the risk of the primary outcome among participants with UACR <30 mg/g, regardless of GFR level (Table). However, compared with participants with GFR ≥60 mL/min/1.73 m² and UACR <30 mg/g, those with UACR ≥30 mg/g had higher risk of the primary outcome at all levels of GFR, with the highest risk observed among those with GFR <45 mL/min/1.73 m². Similar results were observed with the BIS1 equation was used to estimate GFR.

Conclusions: Among older adults without diabetes, increased albuminuria was associated with adverse cardiovascular outcomes at all levels of GFR. However, low GFR was not associated with adverse outcomes in participants with normal albuminuria. These results support the proposal of an age-adapted definition of CKD.

Funding: NIDDK Support

Table

PO2386
Decreased Progression of CKD in Patients Undergoing Fecal Microbiota Transplantation (FMT)
Giovanna Y. Arteaga Muller,1 Adrián Camacho-Ortiz, Elvira Garza-Gonzalez, Samanatha M. Flores-Treviño, Paola Bocanegra-Barias, Graciela C. Fabela-Valdez, Norma Y. Rodriguez-Arroyo. Hospital Universitario Jose Eleuterio Gonzalez Universidad Autónoma de Nuevo Leon, Monterrey, Mexico.

Background: Prevalence of CKD is 8 to 16% in different stages, considered the main cause of emergency and hospital care in Mexico and catastrophic disease, its main causes: diabetes, arterial hypertension and glomerulonephritis. Treatment to prevent progression consists of inhibitors of the renin angiotensin aldosterone system, control of the underlying disease and blood pressure. The estimate of the loss of glomerular filtration rate is 2.3 to 4.5 mL/min per year in CKD patients. The intestinal microbiota has protective, structural and metabolic functions, there is a bidirectional interference of the microbiota and the host maintaining a symbiotic relationship, in CKD patients uremia affects the composition and metabolism of the microbiota, generating dysbiosis that is associated with adverse outcomes. Currently, the effect of the intestinal microbiota in the progression of renal failure is being studied in several clinical trials, carried out at the University Hospital in Monterrey Mexico, in patients diagnosed with CKD due to diabetes and or hypertension, in stages 2, 3, 4 and 5 without renal replacement therapy, divided into 2 groups, MTF group: Microbiota fecal capsules, placebo group: placebo capsules, in both groups 15 capsules were administered every 12 hours for 2 days, on days 0, 10, 30, with a 6-month follow-up to demonstrate the difference in the progression of renal failure.

Results: 28 patients were randomized, the CKD of the placebo group progressed by 53.8% vs 13.3% of the TMF group Fisher’s exact test p value = 0.0418 (Table 1).

Conclusions: The difference in the proportion of patients who did not decrease their GFR at 6 months was statistically significant, in the present study the patients who received FMT had less progression of CKD at 6 months. FMT was associated with a protective factor.

Funding: Private Foundation Support

Table

PO2388
Validation of Novel Cystatin C (CysC) Rapid Measurement Assay with Human Saliva
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Background: Rapid, frequent point-of-care (POC) monitoring of kidney filtration markers such as cystatin C (CysC) that does not require laborious blood specimen draws/processing can improve chronic kidney disease (CKD) patient outcomes and care. Saliva as a non-invasive biobank for monitoring kidney function addresses a clinical need for rapid diagnostics in POC and home-based testing. Emerging data suggests CysC as a more reliable kidney filtration marker than creatinine because it is not affected by age, race, ethnicity, or body mass.

Methods: Our Enhanced Lateral Flow (ELF) immunoassays were validated against a commercial ELISA kit for quantitative measurement of CysC in 76 human healthy and CKD patient saliva samples. We applied Pearson correlation and Bland-Altman analysis to compare the two data sets, and assessed inter-assay repeatability by validating the coefficient of variation (CV) at 5 levels for the samples. Each sample was measured in triplicate (n=3) to obtain the CV value. The ELF assay was tested with 116 samples, and ELISA with 51 samples, due to limited resources.

Results: The ELF assay CysC assessment showed high correlation to the ELISA measurements, with Pearson r=0.78 (Fig. A). Bland-Altman analysis showed a minor bias of -0.017 mg/L between the two assays (Fig. B). Both assays demonstrated a <10% CV for most of the tests, with the ELF assay presenting a lower overall mean CV (6.5%) than the ELISA kit (7.2%) (Fig. C). Data from stability studies verified that the ELF assay maintained functionality at 2-8°C for up to 30 days.

Conclusions: We have demonstrated rapid measurement of CysC in human saliva with our novel ELF assay, with acceptable POC characteristics, and repeatability and reproducibility equivalent to ELISA. The ELF assay provided more accurate and faster

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731
results (<30 min. vs. 3 hr. for ELISA), and also demonstrated a longer shelf life (stable at 510 days at ambient vs. ELISA requirements for storage at -20°C with a 1 yr. expiration date). Future validation studies could lead to a saliva testing framework for kidney function markers, and a potential paradigm shift in the monitoring and care of CKD patients.

**Funding:** NIDDK Support

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**PO2389**

**Kidney Filtration Markers: Accuracy and Reproducibility of Novel Serum Cystatin C Measurements in a Point-of-Care Rapid Test Platform**

*Kamyar Kalantar-Zadeh,* 1 Manal Beslau, 2 Connie Rhee, 1 Trong Nguyen, 2 Maria Ortega, 3 Amy S. You, 1 Rene Amel Peralta, 1 Danh V. Nguyen, 1

University of California Irvine, Irvine, CA; 2Intelligent Optical Systems, Inc., Torrance, CA.

**Background:** Emerging data suggests cystatin C (CysC) as a more reliable kidney filtration marker than creatinine because it is unaffected by age, race, ethnicity, or body mass. In the US, the standard approach to assess blood-based CysC measurements is invasive phlebotomy followed by laborious blood specimen processing. There is a major unmet need for non-invasive point-of-care (POC) measurement of this kidney filtration marker. To fill this gap, we have recently developed and validated novel Enhanced Lateral Flow (ELF) immunoassays to measure CysC in human blood.

**Methods:** Validation of our ELF assays was performed in two steps. First, Pearson correlation and Bland-Altman analysis were used to assess the correlation, agreement and bias of ELF measurements to UCL Medical Center lab standard measurements from a set of 70 serum samples obtained from chronic kidney disease (CKD) patients. Then, Receiver Operating Characteristic (ROC) curve analysis was used to assess the medical diagnostic value of the ELF assay, with ELF assay measurements of 70 CKD samples and 20 healthy reference samples to determine ROC curve and Area Under Curve (AUC) of the assay.

**Results:** The ELF assay measurements showed high correlation to standard lab measurements, with Pearson r = 0.94 (Figure A). Bland-Altman analysis showed bias of -0.5 mg/L for the ELF assay, which could be adjusted if it is consistent when we continue monitoring the assay on a broader concentration set of samples (Figure B). The ROC analysis showed excellent diagnostic value, with AUC=0.83, which shows potential for discriminating healthy and CKD subjects (Figure C and D).

**Conclusions:** We have demonstrated feasibility and validation of a novel POC assay to measure CysC in human blood-based samples. The ELF assay possesses acceptable POC characteristics, correlates well to standard laboratory measurements, and shows good diagnostic value. Future development could lead to a fully available POC measurement framework for CysC as a kidney function marker, and a potential paradigm shift in patient monitoring and care.

**Funding:** NIDDK Support

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**PO2390**

**Serum Creatinine Concentration and Estimates of Muscle Mass Among Race/Ethnicity Groups with End-Stage Kidney Failure**

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**Background:** Racial differences in serum creatinine concentration have been attributed to differences in muscle mass. We examined this hypothesis among End Stage Kidney Disease patients receiving hemodialysis, whose serum creatinine concentration (SCr) should not be highly influenced by glomerular filtration.

**Methods:** 501 participants were enrolled from 2 centers who were at least 1 year post start of hemodialysis and for whom we measured SCr and body composition (including height-adjusted intracellular water [ICW] as a surrogate of muscle mass) using bioelectrical impedance spectroscopy. In multivariable linear regression we examined the independent association of race/ethnicity (Black, Asian, Non-Hispanic White [NHW], and Hispanic) with estimated muscle mass. We then examined whether race/ethnicity was associated with SCr with adjustment for demographics, clinical factors and body composition including ICW.

**Results:** Black (0.24 (-0.01,0.49)) and Hispanic (0.05 (-0.26, 0.37)) participants had similarly higher SCr compared to NHW, but ICW was higher among Asians (0.42 (0.11, 0.72)). In contrast, SCr concentrations were significantly higher among Blacks, Hispanics and Asians compared with NHW. Adjustment for ICW did not change these associations or attenuate the difference in SCr between any racial/ethnic group and NHWs.

**Conclusions:** Among prevalent dialysis participants, ICW, a muscle mass surrogate, was higher among Asian, but not among Black, participants when compared to NHW. After adjusting for ICW, higher SCr was observed across all race ethnicity categories and muscle mass did not appear to explain differences in SCr by race/ethnicity.

**Funding:** NIDDK Support

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**PO2391**

**Patient-Reported Symptoms and Subsequent Risk of Myocardial Infarction in CKD**


University of Washington, Seattle, WA.

**Background:** Patient-reported symptoms often precede clinical acute presentations of atherosclerotic cardiovascular disease (ASCVD), and include chest pain, shortness of breath, and inability to climb stairs. Patients on dialysis frequently have atypical or absent symptoms associated with ASCVD; however, it is unknown whether these same findings are observed in patients with non-dialysis requiring chronic kidney disease. We examined time-updated symptoms of ASCVD and their associations with incident acute myocardial infarction (MI) in a large prospective CKD cohort.

**Methods:** We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study who had available symptom data. Chest pain, shortness of breath, and inability to climb stairs were evaluated using the Kidney Disease Quality of Life Instrument (KDQOL-36) at each annual study visit, and were categorized as “no symptoms,” “mild symptoms” or “moderate to severe symptoms.” Associations between categorical time-updated symptoms and interim MI were assessed using Cox regression models with adjustment for potential confounders. We tested for interaction by prior MI, eGFR, and diabetes.

**Results:** Among 3909 study participants, the mean age was 58 years, and the mean eGFR was 44.3 mL/min/1.73 m2; 22% had prior MI. There were 367 MIs over a median of 7.98 years; median time between symptom assessment and MI was 213 days (IQR 111 to 314 days). Moderate or worse shortness of breath was associated with 1.83-fold increased risk of MI (95% CI 1.25, 2.67) after adjustment. These associations were also seen for chest pain and inability to climb stairs (HR for moderate or worse chest pain 1.65, HR for severe limitation climbing stairs 1.85) (Table). P-values for interaction by prior MI, diabetes, and eGFR were all not statistically significant (p>0.05).

**Conclusions:** Chest pain, shortness of breath, and inability to climb stairs were significantly associated with increased risk of MI in a large cohort of participants with CKD. This highlights the importance of symptom assessment as early warning signs of ASCVD in patients with CKD.

**Funding:** NIDDK Support, Private Foundation Support

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**PO2392**

**SGLT2 Inhibitors: Will They Change the Face of Kidney Care?**


**Background:** This research examines the evolving care and treatment of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), including the introduction and adoption of SGLT2 inhibitors. It includes trending on perceptions across specialists.

**Methods:** A total of 1,030 CKD non-dialysis patient records were collected from 183 nephrologists via an online, HIPAA-compliant form in October and November 2020

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as part of an independent, retrospective chart audit. Data were also collected from an online survey of 74 endocrinologists, 75 cardiologists, and 76 primary care physicians in September and October 2020, and from 105 nephrologists in April 2021.

**Results:** CKD patients often experience a range of comorbidities and treatments throughout their disease. The optimal eGFR level nephrologists report they would initiate a CKD patient on an SGLT2 inhibitor is 57.1 ml/min/1.73m², or early in Stage 3, which is much earlier than the initiation of other treatments such as nutritional vitamin D and ESAs. Upon referral to a nephrologist, one-in-five patients with CKD and T2D are already prescribed an SGLT2 inhibitor; this increases as the patient is under nephrology care, up to nearly one-in-five patients; however, there remains room for substantial growth - most notably in CKD patients without T2D, with just 3% having ever been treated with an SGLT2 inhibitor. While nephrologists have been slow to adopt SGLT2 inhibitors firmly into their treatment paradigms, other physicians report a higher percentage of their DKD patients treated with an SGLT2 inhibitor, especially endocrinologists (34%). One-third of nephrologists report trepidation over prescribing SGLT2 inhibitors in their DKD patients, a percentage that has stayed remarkably consistent over the past year and is nearly mirrored by those who claim they have no trepidation in prescribing. This hindrance only increases (to 44%) when they consider prescribing the agents in non-diabetic CKD patients. However, anticipated use of SGLT2 inhibitors in DKD patients is high across specialists, highlighting the opportunity this class of drugs has to make an impact on the treatment of CKD non-dialysis patients.

**Conclusions:** As SGLT2 inhibitors offer benefits to diabetic and non-diabetic CKD patients, physicians are poised to begin treatment earlier in disease progression, especially with dapagliflozin now approved for CKD patients with and without diabetes.

**PO2392**

**Prescribing Patterns of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with CKD**

**Min Zhu,1,2 Jiahua Li,2 David B. Mount,2 David J. Steele,2 David J. Lucier,3 Malika L. Mendu.2 1Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital Department of Medicine, Boston, MA; 3Massachusetts General Hospital, Boston, MA.

**Background:** Since the publication of the EMPA-REG trial in 2015, sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have been demonstrated to slow chronic kidney disease (CKD) progression in patients with diabetic kidney disease (DKD). More recently in October 2010, the ADA-CKD trial demonstrated SGLT-2i slows CKD progression regardless of diabetes (DM) status. We evaluated the adoption of these novel therapeutics in CKD patients, without and with DM.

**Methods:** A cross-sectional study of the Mass General Brigham Health System CKD registry was conducted in March 2021. All adult patients with non-dialysis CKD stages 3-5 were included. Multivariable logistic regression models were used to assess factors associated with SGLT-2i use in patients without and with DM.

**Results:** Among 49,587 non-DM, CKD patients, only 145 (0.3%) were taking SGLT-2i. Of 22,653 DM, CKD patients, 1,442 (6.4%) were taking SGLT-2i. As shown in the Figure, younger age, Male sex, Black race, history of heart failure, and cardiologist visit in the past year were associated with higher rates of SGLT-2i use in both cohorts. In patients with DM, nephrologist visit in the past year was associated with a higher rate of SGLT-2i use, whereas advanced CKD stages were associated with lower rates of SGLT-2i use.

**Conclusions:** Despite a well-demonstrated benefit of SGLT-2i, the adoption of these novel agents remained extremely low in the CKD population, particularly among patients without diabetes. Given the approval of SGLT-2i in CKD in May 2021, interventions to increase SGLT-2i usage and improve outcomes in patients with CKD are urgently needed.

**Zhuo,1,2 Jiahua Li,2 David B. Mount,2 David J. Steele,3 David J. Lucier,3 Malika L. Mendu.2 1Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital Department of Medicine, Boston, MA; 3Massachusetts General Hospital, Boston, MA.

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**Conclusions:** Despite a well-demonstrated benefit of SGLT-2i, the adoption of these novel agents remained extremely low in the CKD population, particularly among patients without diabetes. Given the approval of SGLT-2i in CKD in May 2021, interventions to increase SGLT-2i usage and improve outcomes in patients with CKD are urgently needed.

**PO2395**

**Treatment with IL-17 Inhibitors Is Associated with Reduced eGFR in Patients with Psoriasis or Psoriatic Arthritis: A Retrospective Cohort Study**

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**Background:** The complex interplay of the cytokines within the IL family can both mediate and modulate inflammation. Specifically, the cytokine IL-17 has been implicated in several disease processes including hypertension, cardiovascular, autoimmune, and chronic inflammatory diseases. However, there is emerging evidence that IL-17 can also favorably modulate inflammation. It has been demonstrated that low-dose IL-17 therapy may prevent and reverse diabetic nephropathy in mouse models. We aimed to study the effect of IL-17 inhibitors on eGFR in human subjects.

**Methods:** We conducted a single-center retrospective cohort study of patients who had been treated with an IL-17 inhibitor (ixekizumab or secukinumab), for the treatment of psoriasis (P) or psoriatic arthritis (PA). Demographics and serum creatinine values were extracted from the electronic medical record. Aggregated data in a 6 month window at 6-months prior to initiation of the IL-17 inhibitor and 12 months after initiation of the IL-17 inhibitor were analyzed using paired t-test. Estimated GFR was calculated using the CKD-Epi equation.

**Results:** We identified 307 patients who had been treated with IL-17 inhibitors. We included 65 patients who had serum creatinine values at pre-specified time periods before and after initiation of treatment. At baseline, the mean age was 50.3±12 years, 43% were men, 51(78%) had a diagnosis of hypertension, 11(17%) had a diagnosis of diabetes, and mean eGFR was 83.6 ml/minute/1.73 m². One year after initiation of IL-17 inhibitor therapy, mean eGFR was significantly lower at 78.7 ml/minute/1.73 m² (p < 0.001). After excluding patients taking medications known to affect eGFR (n=26), there was still a significant decrease in eGFR after 1 year (80.4 versus 83.2 ml/minute/1.73 m², p < 0.01).

**Conclusions:** In patients with P or PA, IL-17 inhibitor therapy is associated with a reduction in eGFR at 1 year after initiation of treatment. Prospective study with longer follow-up is needed to determine the long-term effect of IL-17 inhibitor therapy on kidney function.
PO2396
Network Meta-Analysis for Prevention of Kidney Function Decline Using Uric-Acid-Lowering Therapy in CKD Patients
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Background: Several previous studies have suggested that uric-acid-lowering therapy (ULT) can slow the progression of chronic kidney disease (CKD). However, few studies have evaluated the effects of each ULT treatment on kidney function, although this topic is crucial for CKD patients. This systematic review aimed to summarize evidence from randomized controlled trials (RCTs) concerning the effects of ULT on kidney function.

Methods: We performed a systematic search and selected RCTs in CKD patients comparing the effects of ULT on kidney function. We performed a network meta-analysis to compare each ULT indirectly. The primary outcome was change in estimated glomerular filtration rate (eGFR) from baseline. Treatment effects were summarized using random-effects model.

Results: Ten studies were selected with a total of 1480 patients. Topiroxostat significantly improved eGFR compared to placebo (MD [95% CI]; 1.49 [0.08; 2.90], P = 0.038) (Fig. 1). Although Febuxostat did not show a positive effect overall, it significantly improved eGFR compared to placebo in a subgroup analysis of CKD patients with hyperuricemia (MD [95% CI]; 0.85 [0.02; 1.67], P = 0.045) (Fig. 2). Allopurinol and pegloticase did not show good effects.

Conclusions: Topiroxostat and febuxostat have better renoprotective effects in CKD patients. We believe that the results of this study allow us to recommend ULT with topiroxostat or febuxostat for patients with CKD.

PO2397
Prevalence of Polypharmacy and Associated Adverse Health Outcomes in Patients with CKD: A Systematic Review and Meta-Analysis
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Background: Patients with chronic kidney disease (CKD) are at increased risk of adverse health outcomes associated with excessive medication use (polypharmacy) due to impaired kidney function and multimorbidity. However, data on the associations of polypharmacy and adverse health outcomes in this population are limited. We conducted a systematic review and meta-analysis to determine the prevalence of polypharmacy and its associated health consequences in CKD.

Methods: The study was conducted using a pre-specified study protocol and adheres to PRISMA reporting guidelines. Six electronic databases were searched from inception to September 2020 for studies that included patients with CKD, use of polypharmacy, and associated adverse health outcomes. Random effects models were used to pool the prevalence of polypharmacy and associations with health outcomes.

Results: 53 eligible articles (n = 477,909 patients) met criteria for inclusion. The pooled prevalence of polypharmacy and excessive polypharmacy was 76.2% (95% CI 73.2%;79.1%; range 14.9% to 100%) and 37.4% (95% CI 30.0%-45.2%; range 11.4% to 63.0%), respectively (Figure 1). The prevalence of polypharmacy was 72.7% and 87.1% in non-dialysis CKD and dialysis populations, respectively. 17 studies reported significant associations between polypharmacy and adverse health outcomes. These studies found an increased risk for potentially inappropriate medication use, drug-drug interactions, drug-related problems, medication-related problems, adverse drug reactions, decreased quality of life, decreased kidney function, hospitalization, and mortality.

Conclusions: Polypharmacy is common in CKD and linked to adverse health outcomes. Our findings highlight the need for improved prescribing practices in CKD and the development of strategies to reduce polypharmacy.

Funding: Government Support - Non-U.S.

PO2398
Risk of Bias in Observational Studies Assessing the Relationship Between Proton Pump Inhibitors and Adverse Kidney Outcomes
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Background: Proton pump inhibitors (PPIs) are widely prescribed as acid-suppression therapy. However, some observational studies suggest that long term use of PPIs is potentially associated with adverse kidney outcomes. We assessed potential bias in observational studies reporting on putative associations between PPIs and adverse kidney outcomes. Aki acute interstitial nephritis, AKI acute tubular necrosis, CKD ESRD.

Methods: Searches in EMBASE and PubMed identified relevant English language articles published in the last 10 years. Risk of bias on an outcome-specific basis was evaluated using Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) by 2 independent reviewers (PROSPERO Registration: CRD42021227555).

Results: Of 620 identified records, 26 studies met a priori eligibility criteria and underwent risk of bias assessment. 19 studies were rated as having a moderate risk of bias. 7 studies were rated as having a serious risk of bias, mainly due to inadequate control of confounders and selection bias (Table 1). Effect estimates for the association between PPI and adverse kidney outcomes varied widely (0.24-7.34) but were mostly positive.

Conclusions: Observational studies suggesting kidney harm by PPIs were found to have a moderate to serious risk of bias using the ROBINS-I tool, making it challenging to establish causality. Additional high-quality, real-world evidence among generalizable populations is needed to better understand the relation between PPI treatment and acute/chronic kidney outcomes, taking into account the effects of varying time periods of PPI treatment, potential self-treatment with over-the-counter PPIs, and adequate control for potential critical confounders.

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PO2400

The Association Between the Adherence of Self-Management and Prognosis of Non-Dialysis CKD Stages 3-5 Patients

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Background: Self-management plays a very important role in the prognosis of patients with CKD. However, there is a lack of evidence-based results to support this. This study aimed to evaluate the association between the adherence of self-management and prognosis of non-dialysis CKD stages 3-5 patients.

Methods: Data including basic information, laboratory test results, oral drugs, time of endpoint events were retrospectively collected. Patients were divided into good or poor adherence according to whether they participated in self-management education on time every month. Endpoints were the initiation of renal replacement therapy and death.

Results: 785 patients were included in this study. 111 and 674 patients were considered to have good and poor adherence, respectively. 12 and 162 endpoint events occurred in the good and poor adherence groups. Propensity score matching was performed. After 1:2 matching, the outcomes of 315 patients were analyzed(109 : 206). Univariate Cox regression was performed to screen variables with $P < 0.05$, then we further performed Cox proportional hazards regression with three adjusted models. The results of the 3 models all showed that the good adherence of self-management was an independent factor associated with reduced risk of incident endpoints (HR95%CI: Model 1: 1.077(0.985,1.172); Model 2: 0.978(0.894,1.067); Model 3: 0.934(0.850,1.024)). The Kaplan-Meier analysis demonstrated that the cumulative incidence of endpoint events in the good adherence group was significantly lower than that in the poor adherence group (log-rank test, $P < 0.05$).

Conclusions: This study suggests that good adherence with self-management could effectively reduce the incidence of endpoint events in CKD stages 3-5 patients.
**PO2402**

**Well-Managed CKD and Its Association with Healthcare Resource Utilization and Costs**

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**Background:** Diabetes and hypertension are prevalent in CKD. The association of coordinated care with outcomes in the setting of these coexisting comorbidities is not well understood. This study evaluated the association between well-managed care and healthcare resource utilization (HCRU) and costs.

**Methods:** Using the Humana Research Database, this retrospective cohort study identified 241,628 patients with CKD Stage ≥3 (3% diabetes, 40% hypertension, 50% diabetes and hypertension, 7% neither diabetes nor hypertension) in 2017. Eligible patients were indexed on first evidence of CKD and required to be enrolled in a Medicare Advantage Prescription Drug plan for ≥12 months pre- and post-index date. Patients who had kidney transplant or hospice election pre-index were excluded. Well-managed care measures included hemoglobin A1c (HbA1c) monitoring, adherence to glucose medications, cardiovascular (CV) therapy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), and routine primary care provider (PCP) nephrologist visits. HCRU and costs were evaluated within 12-months post-index.

**Results:** The cohort was 55% female, 77% White, average age of 75 years, and comprised of 67%, 23%, 10%, and 1% patients with Stages 3a, 3b, 4, and 5 CKD, respectively. Patients with diabetes and hypertension who were adherent to well-managed care were significantly less likely to experience an inpatient (IP) admission or emergency department (ED) visit (Table 1) and incurred lower mean monthly costs compared with patients who were not adherent to well-managed care. Similar results were observed for patients with diabetes only, hypertension only, or neither condition.

**Conclusions:** Well-managed diabetes and/or hypertension in patients with CKD was associated with lower HCRU and costs. Findings may inform innovative models of CKD care coordination.

**Measure of well-managed care**

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<th>Measures of well-managed care</th>
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<tr>
<td>HbA1c monitoring</td>
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<td>Adherence to glucose medications</td>
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<td>Cardiovascular therapy</td>
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<td>Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs)</td>
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* ACEi/ARBs not significant

**PO2404**

**CKD Healthcare Utilization Preceding Unplanned Dialysis in a Large Accountable Care Organization**

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**Background:** Unplanned dialysis initiation or “crash starts” is associated with worse outcomes and higher costs in chronic kidney disease (CKD). Avoiding these events should be a quality improvement priority for accountable care organizations (ACOs). We examined care utilization associated with unplanned dialysis initiation in a large ACO.

**Methods:** We evaluated 77,593 CKD patients with stage 5 CKD in the Teal-Vet clinical registry. The study cohort was comprised of veterans who received care at the Cleveland Veterans Affairs Health System. Subsets were based on enrollment in a comprehensive pre-end stage kidney disease (CPE) education program versus a standard care program. We evaluated patients for crash start (initiation of dialysis in patients with stage 5 or 4 chronic kidney disease) and emergency department visits within 30 days of the crash start event. We assessed the association of enrollment in the CPE education program with unplanned dialysis initiation using a logistic regression model.

**Results:** Of the total of 226 randomly selected Veterans mail-invited for study participation over the initial 15 months, approach success rate was 3.5% (n=9) for opt-in versus 20.2% (n=45) for opt-out approach. The study staff were able to approach 157 invites (success rate of 72.4%), resulting in 86 (54.8%) enrollments, while 10 (18.8%) requested unenrollment. A total of 77,593 CKD patients were evaluated. Crash start patients had higher rates of unplanned hemodialysis (47.7%) compared to standard care patients (31.4%). Crash start patients initiated dialysis with outpatient HD or peritoneal dialysis (PD). Those with acute kidney injury, hospital death, urgent PD, or preemptive transplant were excluded. Of the total of 226 randomly selected Veterans mail-invited for study participation over the initial 15 months, approach success rate was 3.5% (n=9) for opt-in versus 20.2% (n=45) for opt-out approach. The study staff were able to approach 157 invites (success rate of 72.4%), resulting in 86 (54.8%) enrollments, while 10 (18.8%) requested unenrollment. A total of 77,593 CKD patients were evaluated. Crash start patients had higher rates of unplanned hemodialysis (47.7%) compared to standard care patients (31.4%).

**Conclusions:** Patient driven opt-in approaches are less effective and efficient for enrollments in clinical and research activities involving the universally recommended service-like kidney disease education.

**Funding:** Veterans Affairs Support

**PCP = primary care provider**

**PO2405**

**Comparing Tele nephrology (TN) vs. Face-to-Face (F2F) Visits: A Comprehensive Outpatient Nephropathy Patient Perspective-Based Evaluation**


**Background:** Little is known about patient perspectives on the quality of care provided via TN compared to F2F visits. We aimed to use objective survey data to study patients’ perspectives on outpatient nephropathy care received via TN (phone and video) versus F2F visits.

**Methods:** We retrospectively studied adults who received outpatient nephropathy care at Mayo Clinic, Rochester, MN, from March 1st – July 31st 2020. We used a standardized structured survey methodology to evaluate patient satisfaction across TN versus F2F visits. The primary outcome was the percent of patients who responded with a score of good (4) or very good (5) on a 5-point Likert scale on survey questions that asked their perspectives with regard to access to their nephrologist, their relationship with care provider, and when relevant – their opinions on the tele nephrology technology, and

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

736
their overall assessment of the care they received during the nephrology visit. Wilcoxon rank sum tests and chi-square tests were used as appropriate to compare tele nephrology versus face-to-face visits.

**Results:** 3,486 of the patient encounters were face-to-face, 808 via phone and 317 via video. 443 patients responded to satisfaction surveys, and 21% of these had TN encounters. Established patients made up 79.6% of TN and 60.9% of F2F visits. There was no statistically significant difference in patient perceived access to health care, satisfaction with their care provider, or overall quality of care between patients who received care via TN versus F2F.

**Conclusions:** Patient satisfaction was equally high amongst those patients seen face-to-face or via tele nephrology.

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**PO2406**

**Depressive Symptom Trajectory and CKD Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study**

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**Background:** While depressive symptoms (DS) are highly prevalent in adults with early-stage chronic kidney disease (CKD), little is known about its course over time. We identified trajectories of DS and evaluated their association with CKD progression in adults with CKD enrolled in the CRIC study.

**Methods:** DS were assessed using the Beck Depression Inventory (BDI), at baseline and biennially. Higher BDI scores are consistent with more severe DS. Glomerular and tubulointerstitial diseases have been associated with inflammatory bowel disease (IBD), ulcerative colitis, UC and Crohn’s disease, CD. However, the clinical outcomes of UC and CD patients who underwent kidney biopsy are not well described. We present a case series of the kidney biopsy findings and clinical outcomes for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUsSupport.aspx, Private Foundation Support, Government Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUsSupport.aspx, Private Foundation Support, Government Support - Non-U.S.

**PO2407**

**Health-Related Quality of Life and Depression Score Differences in Brazilian and US CKD Patients**

Danwen Yang1, Lisa Henn,2 Daniel G. Muenz,2 Brian Bieber,2 Antonio A. Lopes,1 Elodie Speyer,3 Bruce M. Robinson,2 Roberto Pecoits-Filho,2 Ronald L. Pisoni,3 Fredric O. Finkelstein,1 Yale University School of Medicine, New Haven, CT; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Universidade Federal da Bahia, Salvador, Brazil; 4INSERM, Paris, France.

**Background:** CKD patients suffer from many issues, increasing in prevalence and severity as disease progresses, that may affect their perceptions of health-related quality of life (HRQOL) and increase depression symptoms (DS). A patient-centered care approach including systematic assessment of self-reported HRQOL and DS as CKD progresses facilitates tailoring the treatment to individual patient concerns. This study examines the relationship at baseline between CKD stage and patient responses to the KDQOL-36 and CESD-10.

**Methods:** We studied 1,901 CKDOPPS participants (629 Stage 3, 1,009 Stage 4, and 263 Stage 5) from Brazil (n=598) and the U.S. (n=1,310). Patients at different CKD stages at study selection were compared for differences at baseline in scores of DS (CESD-10 [Kohout, higher score worse, max 40]) and HRQOL (KDQOL-36, higher score better, each scale max 100). The KDQOL-36 yields the Physical Component Summary (PCS) and Mental Component Summary (MCS) from the SF-12v1; Burden of Kidney Disease (BKD); Symptoms of Kidney Disease (SKD); and Effects of Kidney Disease (EKD). The Kruskal-Wallis Test assessed differences among groups.

**Results:** Patients’ mean age, albumin, and BP did not differ in the 3 CKD groups. Mean HbA1c was lower for CKD 5 (10.8) and 4 (11.9) than for CKD 3 (12.7) patients, but only slight mean difference occurred in DS and MCS by CKD stage. Mean PCS score was 39.8 and 37.9 in CKD 3 and 5 respectively. The largest mean difference in HRQOL scores by CKD stage was for BKD: 77.7 in CKD 3, 69.4 in CKD 4, and 58.0 in CKD 5 (p < 0.0001). Lower HRQOL scores for more advanced CKD stages occurred for EKD: (85.13, 79.7, and 76.0 in CKD 3, 4, and 5, p<0.0001) and SKD (79.95, 77.8, 77.1, p=0.0007). Compared to U.S. patients, those in Brazil had higher PCS scores (40.1 vs 37.5) but lower BKD scores (62.5 vs 74.4); other scores did not differ by country.

**Conclusions:** HRQOL baseline scores for CKD patients show a greater difference in the BKD scores; differences by CKD stage were not seen in MCS and CESD-10 scores; and minimal difference occurred for PCS scores. These results potentially can help address patients’ problems and concerns at different CKD stages.

**Funding:** Other U.S. Government Support, Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. Funders included those who had UC or CD diagnosed by gastroenterology evaluation and biopsy. Kidney biopsy data including primary and secondary diagnoses, degree of interstitial fibrosis and tubular atrophy (IFTA), and degree of arteriosclerosis were extracted from biopsy reports. Incident end-stage kidney disease (ESKD) was defined as requirement of renal replacement therapy. All analyses were performed using SAS.

**Results:** Of 59,007 patients with an ICD code of inflammatory bowel disease, 66 patients had kidney tumor biopsies and 140 patients (91 with UC and 49 with CD) underwent biopsy to evaluate intrinsic kidney disease. At the time of kidney biopsy, the mean serum creatinine was 2.9 mg/dL for UC and 3.4 mg/dL for CD and the mean

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Patterns of Progression of Stage 2 CKD and Associated Costs in Medicare Advantage Enrollees

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Background: The prevalence of chronic kidney disease (CKD) in Medicare beneficiaries has quadrupled in the past two decades. Little is known about progression of CKD in older adults with early CKD. We identify CKD progression trajectories, risk factors and healthcare costs for these trajectories in a large cohort of Medicare Advantage (MA) enrollees with stage 2 CKD.

Methods: In a cohort of 418,930 MA enrollees, we identified trajectories of stage 2 CKD progression (measured by eGFR) from 2014-2018 via group-based trajectory modeling. Multinomial logistic regression was used to identify patient factors associated with each trajectory. Mean total costs one year before and two years after baseline are described.

Results: The cohort had a mean age of 72.6 years, was predominantly female (57.2%) and White (67.8%), and had mean baseline eGFR of 75.3 ml/min/1.73 m². Median follow-up was 2.6 years. We identified 5 trajectories of kidney function: stable function (22.1%); slow decline with mean baseline eGFR 78.3 (30.1%), slow decline with mean baseline eGFR 71.0 (28.5%); steep decline (16.4%); accelerated decline (2.9%). In adjusted analyses, higher odds of accelerated decline (vs. stable kidney function) were found in those age 75 and older, (odds ratio (OR)=2.84, 95% confidence interval (CI): 2.38-3.38), living in a non-metropolitan area (OR=1.26, 95% CI: 1.18-1.35), with lower eGFR at baseline (OR=0.64, 95% CI: 0.63-0.64), greater comorbidity (OR=1.28, 95% CI: 1.27-1.29), having a nephrologist visit (OR=2.06, 95% CI: 1.81-2.34) or clinical diagnosis of CKD (OR=4.41, 95% CI: 4.11-4.74) during the year prior to baseline. Mean total MA costs of enrollees with accelerated kidney function decline were nearly twice as high as costs of MA enrollees in the other 4 trajectories in every year ($27,856 versus $13,507) for stable kidney function during the first year.

Conclusions: The small fraction of MA enrollees with accelerated loss of kidney function have disproportionately higher costs than other enrollees with stage 2 CKD and may benefit from closer clinical management to minimize progression and contain costs.

Funding: Other U.S. Government Support
PO2413
Association of Kidney Function with Major Postoperative Events After Noncardiac Ambulatory Surgeries: A Population-Based Cohort Study

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Background: Though people with chronic kidney disease (CKD) frequently receive outpatient surgical procedures, the associated risks of major perioperative outcomes is unknown. In this study, we estimated the association between estimated glomerular filtration rate (eGFR) and a composite of acute myocardial infarction (AMI) or death after ambulatory non-cardiac surgery.

Methods: This retrospective population-based cohort study used administrative health and laboratory data from Alberta, Canada, and included adults with measured preoperative kidney function undergoing ambulatory non-cardiac surgery between April 2005 and February 2017. We categorized participants into six eGFR categories (in mL/min/1.73 m 2) of ≥ 60 (G1-2), 45-59 (G3a), 30-44 (G3b), 15-29 (G4), < 15 not receiving dialysis (G5D), and those receiving chronic dialysis (GSD). The odds of AMI or death within 30 days of surgery were estimated using multivariable generalized estimating equations. Secondary outcomes included the odds of hospitalization, emergency department (ED) and urgent care (UC) visits.

Results: We identified 543,160 procedures in 323,521 people with a median age of 66 years (IQR 56-76); 52% were female. Overall, 2,338 people (0.7%) died or had an AMI within 30 days of surgery. Compared with the G1-2 category, the adjusted odds ratio (OR) of death or AMI increased from 1.1 (95% Confidence interval [CI]: 1.0, 1.3) for G3a to 3.1 (CI: 2.6, 3.6) for GSD. The associations between eGFR and the independent components of this outcome were consistent for both death and AMI, and similar for 30-day hospitalization. ED and UCC visits within 30 days were frequent (17%), though similar across eGFR categories.

Conclusions: We found that ambulatory surgery was associated with a low overall risk of major postoperative events, though was significantly higher for people with CKD. This study may inform their perioperative shared decision-making and management, and support more refined resource allocation and intervention approaches based on eGFR may be warranted.

Funding: Government Support - Non-U.S.

PO2414
Association of Multimorbidity and Mortality Risk in US Veterans with New-Onset CKD

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Background: Many patients with CKD live with multiple chronic conditions. We examined the association among multimorbidity and 10-year risk of death in US veterans with incident CKD.

Methods: The cohort included 389,005 veterans with new-onset CKD (estimated GFR<60 mL/min/1.73 m 2 for ≥3 months) between 2004 and 2018 in the US Veterans Health Administration, followed for up to 10 years or December 31, 2018. Multimorbidity was measured by the total number of comorbidities among 16 conditions based on ICD-9/ICD-10 codes during the 2 years before and up to 6 months after CKD onset, and categorized as 0–1, 2, 3, 4, 5, 6, 7, and ≥8 conditions. We estimated mortality risk by age group at 10-year CKD onset.

Results: The median number of comorbidities at CKD onset was 4 (interquartile range: 3-6). After multivariable adjustment, the association between increasing multimorbidity and mortality risk was seen in all age groups, but was stronger in younger than older veterans (Table). Death risk when having ≥5 comorbidities was 8-fold higher in ages 18-44, but only 2-fold higher in ages 85-100, compared to their age counterparts with 0 comorbidity. Multimorbidity patterns also differed by age. For example, among those with obesity ≥2 concurrent comorbidities most frequently in ages 18-44, as compared to hypertension and cardiovascular disease in older age groups.

Conclusions: At CKD onset, 95% of patients had multiple comorbidities. The association of multimorbidity and mortality was greater for younger patients. Effective plans for early CKD diagnosis and timely treatment of comorbidities may improve survival in CKD, especially for younger patients.

Funding: NIDDK Support, Other U.S. Government Support

PO2415
Self-Reported Walk Pace and Cardiovascular Events in Adults with CKD

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Background: Physical function, as measured by self-reported walk pace, is lower in patients with CKD compared to the general population. While slower walk pace has been found to be associated with cardiovascular outcomes in non-CKD populations, its relationship to cardiovascular outcomes in CKD patients has not been fully explored.

Methods: We used data from 3925 adults with mild-to-moderate CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. Walk pace (scored 0-4) was self-reported using the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey. Outcomes included atherosclerotic events (a composite of myocardial infarction, stroke or peripheral arterial disease), incident heart failure, all-cause death, and cardiovascular death. Multivariable Cox proportional hazard models with time-updated covariates were used to evaluate the association of walk pace with outcomes.

Results: At baseline, mean age was 58 years, 45% were women, 33% had self-reported cardiovascular disease, mean eGFR was 45 ml/min/m2, 12% reported brisk or striding walk pace (>3 mph), 39% reported average walk pace (2-3 mph), and 48% reported walked pace of none or casual (<2 mph). During a median follow-up of 11.5 years, there were 732 atherosclerotic events, 790 incident heart failure events, 1333 deaths from any cause, and 434 cardiovascular deaths. In fully adjusted models, there was a graded association between walk pace and risk for each outcome (Figure).

Conclusions: In this cohort of adults with CKD, faster self-reported walk pace was associated with lower risk of cardiovascular events and mortality. These findings may have implications for risk stratification, as well as for future interventions targeting physical function in patients with CKD.

Funding: NIDDK Support
PO2416

Low Magnesium Predictors of Cardiovascular Outcomes in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: There are few large-scale studies of the association between magnesium (Mg) and cardiovascular (CV) outcomes in pre-dialysis chronic kidney disease (CKD) patients. Therefore, we analyzed the effects of Mg on CV outcomes in a large-scale cohort of pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and CV outcomes in a prospective, multi-center cohort of pre-dialysis CKD patients (n=1,646). Patients were divided into four groups according to serum Mg concentration. The primary endpoint was composite outcome, defined as either a CV event and/or all-cause death. Secondary outcomes were coronary artery calcification (CAC) progression and arterial stiffness progression as assessed by mean brachial-ankle pulse velocity (baPWV).

Results: During a median follow-up of 6.0 years, 196 (11.9%) patients had the composite outcome of a CV event and/or all-cause death. In a multivariable analysis, a specific model, patients in the lowest Mg group (serum Mg <2 mg/dL) had an elevated risk of a composite outcome (hazard ratio (HR) 1.71 [1.02-2.84]; P=0.038; serum Mg ≥2.2 mg/dL as the reference group). Subgroup analyses showed that low Mg was particularly associated with risk of a composite outcome in patients with early CKD and those who were male. Patients in the lowest Mg group also had increased risks of progression to CAC and arterial stiffness relative to the reference group (Mg ≥2.2 mg/dL).

Conclusions: Low Mg level is a predictor of cardiovascular outcomes in pre-dialysis CKD patients.

PO2417

Baseline Renal Function and Left Ventricular Assist Device Outcomes

Among Patients with CKD

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Background: Chronic kidney disease (CKD) is associated with increased risk of cardiovascular disease. Coronary artery disease is one of the most important causes of heart failure with reduced ejection fraction, a condition for which advanced therapies such as left ventricular assist device (LVAD) and orthotopic heart transplant (OHT) are increasingly utilized. Information about outcomes of CKD patients with LVADs is limited. We studied the outcomes of patients with CKD who had received LVAD in a large cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated electronic medical records network, to identify 4939 patients ages 18 years and older with heart failure who were referred to 31 healthcare organizations, from the United States, who had received LVAD implantation between 1/1/2010 and 12/31/2019. We included 1552 patients with estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m². We grouped the eligible patients into stages of CKD, based on eGFR: stages: 2 (n=1140), 3a (n=921), 3b (n=563), 4 (n=118), and 5 (n=601)). The primary and secondary outcomes were survival and receiving an OHT within one year of LVAD implantation, respectively. We used CKD stage 2 as the reference and calculated the odds ratio (OR) with [95% confidence interval (CI)] of each of the two outcomes.

Results: A total of 172 patients died within one year of LVAD implantation. When compared with Stage 2 CKD, and after propensity score matching, there was a decrease in the OR of survival at one year with higher stages of CKD: —Stage 3b: OR: 0.64 (CI: 0.41, 0.99), —Stage 4: OR: 0.62 (CI: 0.24, 1.57). —Stage 5: OR: 0.57 (0.38, 0.86). These results were significant in the odds of survival between stage 3a and the reference group. A total of 274 heart transplants were performed within the first year after LVAD implantation. Patients in the reference group were more likely to receive an OHT within the first year in comparison with CKD stage 5 patients (OR: 1.61; CI: 1.06, 2.45).

Conclusions: CKD stage 2 is a more advanced stage of CKD that is associated with decreased survival in LVAD patients. Patients with CKD stage 2 are more likely to undergo OHT compared to those with CKD stage 5.

PO2418

Associations of eGFR and Albuminuria with Physical Performance

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Background: Reduced physical performance is associated with increased all-cause mortality, and individuals with chronic kidney disease (CKD) are at an increased risk of suffering from impaired physical function. However, most studies have not included lab-based surrogate measures may be used as early indicators of hard clinical outcomes.

Methods: The Brain in Kidney Disease (BRINK) cohort was designed to examine cognitive and physical function among adults with CKD. Intentional recruitment criteria were used to recruit participants with an eGFR (ml/min/1.73m²) range from <30 to 59 included, in addition to a control group with eGFR ≥60. We estimated GFR using creatinine (eGFRcreatinine) and, in separate analyses, cystatin C (eGFRcystatinC), and measured urine albumin to creatinine ratio (UACR). We assessed physical performance using the Short Physical Performance Battery (SPPB, range: 0-12). 571 community-dwelling adults with baseline SSPB scores were included. Univariate and multivariable logistic regression models, adjusted for demographics and comorbidity, examined associations of eGFR and UACR with SPBP <10.

Results: Mean age was 69.3 years. 157 (27.5%) participants had eGFR <30, 376 (48.2%) had eGFR 30 to <60, and 138 (24.2%) ≥60. In separate univariate analyses, both lower eGFR and higher UACR were associated with higher odds of low SPBP (Table). In the adjusted model with eGFR, UACR and covariates, UACR retained a significant association with low SPBP, but eGFR, did not. Similar results were found in models with both eGFR and UACR.

Conclusions: Both low eGFR, and high UACR were associated with poor physical performance in univariate analyses, but only UACR remained associated in the fully adjusted model. Similar results with eGFR, suggest that confounding based on muscle mass does not explain the lack of association between eGFR, and physical performance and raises the possibility that vascular or endothelial function may be important factors.

Funding: NIDDK Support, Other NIH Support - NIA

PO2419

Association Between Estimated Glomerular Filtration Rate Decline and Clinical Outcomes in Non-diabetic CKD

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Background: There is limited evidence on association between surrogate laboratory endpoints and hard clinical outcomes in chronic kidney disease (CKD). This real-world data analysis investigated dependence between relative estimated glomerular filtration rate (eGFR) decline of ≥30%, ≥40%, and ≥57% and cardiovascular outcomes in non-diabetic CKD patients treated in routine clinical practice.

Methods: Individual-level data from the US claims database, Optum Clinformatics Data Mart (CDM), for years 2008 – 2018 were analysed. Adult individuals were required to have kick stage 3 or 4 (index date), 365 days of continuous insurance prior to index (baseline period). Individuals with diabetes mellitus, CKD stage 5 or end-stage kidney disease (ESKD) prior index or kidney failure, transplant or dialysis in the baseline period were excluded. Patients were followed until insurance/data end, or death. Two selected hard clinical outcomes were hospitalisation for heart failure (HHF) and a composite of ESKD/kidney failure/need for dialysis. To investigate the association between eGFR decrease and clinical outcomes, an intercurrent event analysis was performed using eGFR decline of ≥30%, ≥40%, or ≥57% as an intercurrent event.

Results: Of 64 million individuals in Optum CDM, 504,924 satisfied the selection criteria, median age 75 years, 60% female, 10% black. At baseline, eGFR values were available for 62% of individuals; median eGFR was 53, 94% of those patients had at least one eGFR value in the follow-up period of a median 744 days. Proportion of the patients with eGFR decline of ≥30%, 40%, 57% was 5%, 3% and 1%. More rapid eGFR decline was associated with increased risk of the outcome. The hazard ratio for HHF was 3.03, 3.41, 3.86 and for ESKD/kidney failure/need for dialysis it was 5.61, 8.29 and 16.83 in patients with eGFR decline of ≥30%, ≥40%, ≥57% compared to those with no such decline, respectively.

Conclusions: In this analysis of the US non-diabetic CKD patients treated in routine clinical practice, a relative eGFR decline of ≥30%, ≥40%, ≥57% was associated with a substantial increase in HHF and ESKD/kidney failure/need for dialysis, supporting that carefully selected lab-based surrogate measures may be used as early indicators of hard clinical outcomes.

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PO2420

Effect of Obesity and Metabolic Dysfunction on Cardiovascular Events and Progression to ESRD in CKD

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Background: Obesity and metabolic dysfunction increased the risk of cardiovascular event and chronic kidney disease (CKD) progression. However, there are conflicting results on clinical outcomes in obese patients without metabolic dysfunction and it is unclear whether metabolically healthy obesity increases the risk of cardiovascular events and progression to end-stage renal disease in CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: We enrolled 166,397 CKD patients from Korea National Health Insurance Service between January 2009 and December 2011. Obesity was defined as body mass index greater than 23kg/m². Metabolic dysfunction was assessed using components: waist circumference, blood pressure, fasting blood sugar, triglyceride level, high-density lipoprotein cholesterol level. The primary endpoint was the ischemic heart disease, ischemic stroke and progression to end-stage renal disease (ESRD).

Results: Of total CKD patients, the proportion of patients with metabolic dysfunction was significantly higher in obese patients than in non-obese patients (25.3% vs. 5.4%; p < 0.001). The progression analyses compared to metabolically healthy non-obese patients, metabolic dysfunction significantly increased the risk of ischemic heart disease and progression to ESRD in patients with and without obesity. Patients with metabolically healthy obesity were significantly associated with increased risk of ischemic heart disease (HR 1.22; 95% CI 1.00-1.50) and ischemic stroke (HR 1.48; 95% CI 1.10-1.99). However, the risk of progression to ESRD was not significantly increased (HR 0.98; 95% CI 0.87-1.10).

Conclusions: The metabolic dysfunction was significantly associated with worse clinical outcomes in CKD patients, irrespective of obesity. The metabolically healthy obesity increased risk for ischemic heart disease and ischemic stroke, but not for progression to ESRD.

PO2421
Diet Quality and Kidney Outcomes in Adolescent and Adult Americans: The Strong Heart Family Study
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Background: The burden of chronic and end stage kidney disease (CKD and ESKD), is exceedingly high amongst American Indians (AI). We sought to examine the relationship of diet quality, a modifiable risk factor, and kidney outcomes in AI adolescents and adults, hypothesizing that poorer quality diets would be associated with incident albuminuria and accelerated eGFR decline in this population.

Methods: This is a secondary analysis of data from the Strong Heart Family Study, a longitudinal study of cardiovascular disease and its risk factors among AIs from Arizona, North and South Dakota, and Oklahoma (n=1721, mean age 39 ±16 years, 16% adolescents aged 14-21 years, 61% female, 28% with hypertension, 13% with diabetes, 52% with obesity, 4% with CKD at baseline). Participants completed two exams (baseline: 2001-2003; follow-up: 2007-2009). The primary exposure (at baseline) was the Alternative Healthy Eating Index (AHEI), a measure of diet quality on a 110-point scale (baseline: 2001-2003; follow-up: 2007-2009). The primary outcomes (at follow-up) were: 1) incident albuminuria (albumin to creatinine ratio ≥30mg/g); 2) eGFR decline of 30%. Generalized estimating equations were used to examine the association of AHEI (in quartiles) with incident albuminuria and eGFR decline.

Results: In total, 9.9% (5.6% of adolescents) had incident albuminuria and 5.6% of participants (9.2% of adolescents) had eGFR decline of 30%. Median AHEI for the poorest diet quartile was 34 compared to 55 for the healthiest diet quartile, each 10-20 points lower than AHEI scores from studies of the general population. The unadjusted odds ratio (OR) for incident albuminuria comparing extreme quartiles of diet quality (poorest versus healthiest [reference] quartiles) was 1.32 (95%CI 0.92, 1.89). After adjustment for baseline diabetes, eGFR and age, the OR for incident albuminuria was 1.79 (95% CI 1.24, 2.58). There were no significant unadjusted or adjusted associations of diet quality with eGFR decline.

Conclusions: These preliminary results suggest an association of diet quality and incident albuminuria in AI. Given the high burden of CKD in this population, further research is required to determine whether interventions to improve diet quality may improve kidney outcomes.

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PO2422
Renal Function and Effect of Body Mass Index on Mortality Risk After Acute Myocardial Infarction
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Background: Obesity is paradoxically linked to greater survival benefit after acute myocardial infarction (AMI). In patients with renal impairment, higher body mass index (BMI) is also associated with protective effects against cardiovascular and all-cause mortality. However, there are no studies investigating the interactive effects of BMI and renal function on mortality risk after AMI.

Methods: We enrolled 12,647 AMI patients from Korea Acute myocardial Infarction Registry between November 2011 and December 2015. Patients were categorized based on renal function; normal (90 ml/min/1.73m²), mild (90-45 ml/min/1.73m²), and moderate impairment (<45 ml/min/1.73m²). BMI was divided into four groups; underweight (<18.5 kg/m²), ideal (18.5-23.5 kg/m²), overweight (23.5-25 kg/m²) and obesity (≥25 kg/m²). The primary endpoint was 2-year mortality after AMI treatment.

Results: In multivariable Cox-regression analysis, compared to ideal weight patients, overweight and obese patients were associated lower risk of mortality and underweight patients had the increased risk of mortality in all renal function categories. However, the survival effect of each BMI stratum was decreased as renal function worsened. The adjusted mortality risk of obesity was 0.63 (95% CI 0.041-0.99), 0.76 (95% CI 0.59-0.97) and 0.84 (95% CI 0.65-1.08) for patients with normal, mild and moderate renal function impairment, respectively. There was a significant interaction between BMI and renal function (P = 0.010). We found that the survival benefit of obesity for noncardiac death was decreased with decreasing renal function (P for interaction = 0.03), but obesity-related advantage was not changed between different renal function (P for interaction = 0.03).

Conclusions: The effect of BMI on mortality risk after AMI was dependent on renal function. The association between greater BMI and survival benefit was weakened as renal function was worsened. We suggest that the association between renal function and effect of BMI on mortality originated in non-cardiac, not cardiac death.

PO2423
Steroid-Resistant Retropertional Fibrosis in the Elderly
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Introduction: Retropertionial fibrosis (RFP) is a rare disease characterized by chronic inflammation and fibrosis that involve multiple organs, including the ureters leading to obstructive uropathy. IgG4-related RFAP accounts for the majority of cases. We present a case of obstructive uropathy secondary to RFP that is steroids resistant

Case Description: A 71-year-old male known case of atrial fibrillation on warfarin presents with urinary hesitancy and decrease output. No history of fever, weight loss or night sweats. His creatinine was 1.8mg/dL from baseline of 0.9mg/dL. A CT scan of the abdomen revealed a 15x14cm retroperitoneal lesion extending from aortic bifurcation and obstructing both ureters with moderate left-sided hydronephrosis. The patient required double J-stent (DIS) placement with no improvement in creatinine. Workup revealed elevated IgG4 levels (1215mg/L), normal CBC, negative quantiferon test. Chest X-ray, malignancy screening and PET scan were unremarkable. The patient refused the biopsy given the risk of bleeding. He was started on prednisolone 80 mg for one month with no improvement of hydronephrosis. The patient developed hypertension, hyperglycemia, and edema, hence switching to mycophenolate mofetil (MMF) with low-dose prednisone. Repeated CT scan showed a partial reduction in retropertional fibrosis (12x13cm) with mild hydronephrosis

Discussion: Although rare, secondary causes of RFP such as tuberculosis, Castleman disease, Erdheim-Chester disease, lymphoma and bladder carcinoma should be identified. In idiopathic RFP, high-dose glucocorticoids are the first line of treatment. Several studies have shown the effectiveness of low-dose steroids in combination with immunosuppressive drugs like MMF or rituximab. The use of a combination treatment as a first-line treatment is still debatable, however, patients who cannot tolerate high doses of prednisolone and have poor treatment response should be considered for alternative therapy.
Methods: We recruited 13 participants with eGFR<60 ml/min/1.73m². Cardiopulmonary fitness (absolute VO2 peak), total work performed, and work efficiency were measured using COSMED K5 wearable metabolic system during cycle ergometry testing. PBMC bioenergetics analysis were performed using the high resolution respirometry (Oroboros O2k). PBMC oxygen consumption rate was measured with secretory additions of pyruvate, oligomycin, FCCP, and antimycin A. We estimated basal, maximal uncoupled respiration (MUR) and spare respiratory capacity (SRC). SRC was defined as the difference between basal respiration and MUR. Pearson correlation coefficient was used to assess correlation of PBMC bioenergetics with muscle performance.

Results: The mean age of participants was 60.6 +/-9.5 years, eGFR was 35.3 +/-12.5 ml/min/1.73m² and 53% were females. PBMC MUR correlated with total work (r=0.57, P-value=0.041) and efficiency (absolute) (r=0.58, P-value=0.034). PBMC SRC correlated with total work (r=0.58, P-value=0.036) and efficiency (r=0.60, P-value=0.029). VO2 peak correlated with PBMC basal respiration (r=0.56, P-value=0.041), MUR (r=0.69, P-value=0.007), and SRC (r=0.71, P-value=0.006).

Conclusions: These results suggest that PBMC respiration is strongly associated with exercise capacity and efficiency. Further studies are needed to investigate biologic determinants of PBMC bioenergetic health and its validity as a surrogate marker of skeletal muscle metabolic health in CKD.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

Figure 1. Association of PBMC reserve capacity with A) total work efficiency and B) cardiorespiratory function (VO2 peak).

PO2425
Association of Proximal Tubular Secretory Clearance with Decline in Cognitive Function
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Background: Persons with chronic kidney disease (CKD) are at risk for cognitive decline. The retention of protein bound organic solutes, normally cleared by renal tubular secretion, is hypothesized to contribute to cognitive dysfunction in CKD. We tested whether lower kidney clearance of secretory solutes is associated with cognitive decline in a multi-center CKD cohort.

Methods: We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study, excluding persons with prior stroke or baseline cognitive impairment. We estimated tubular secretory clearance by 24-hour kidney clearance of eight solutes primarily eliminated by tubular secretion. Cognitive function was measured by annual Modified Mini Mental Status (3MS) exams. We defined cognitive decline as a sustained >5 point decrease in the 3MS score from baseline. Associations were assessed with Cox survival models; we controlled for multiple comparisons by calculating q-values.

Results: Among 2366 study participants, the mean age was 58 years, mean eGFR was 35 +/-12.5 ml/min/1.73m² and 53% were females. PBMC MUR correlated with total work (r=0.57, P-value=0.041) and efficiency (absolute) (r=0.58, P-value=0.034). PBMC SRC correlated with total work (r=0.58, P-value=0.036) and efficiency (r=0.60, P-value=0.029). VO2 peak correlated with PBMC basal respiration (r=0.56, P-value=0.041), MUR (r=0.69, P-value=0.007), and SRC (r=0.71, P-value=0.006).

Conclusions: These results suggest that PBMC respiration is strongly associated with exercise capacity and efficiency. Further studies are needed to investigate biologic determinants of PBMC bioenergetic health and its validity as a surrogate marker of skeletal muscle metabolic health in CKD.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

Figure 1. Association of PBMC reserve capacity with A) total work efficiency and B) cardiorespiratory function (VO2 peak).

PO2426
Clinical Features and Outcomes of Immunoglobulin G4-Related Disease Including Kidney Involvement
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Background: Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized disease, and a few epidemiologic studies about this disorder have been published. This research aimed to describe the clinical, laboratory, and histopathological features and outcomes of IgG4-RD.

Methods: Ninety-four patients who satisfied the comprehensive diagnostic criteria on IgG4-RD were included in this study. Fifty-eight (61.7%) were men. The mean age was 54.8 years, and the median follow-up duration was 32.9 months. The clinical feature between single and multiple organ involvement and with or without kidney involvement groups were evaluated based on symptoms and laboratory findings. The clinical outcome was assessed according to treatment strategies and response.

Results: Of 94 patients, 56 (59.6%) had multiple organs involvement. It showed a variety of symptoms and organs involved. Patients with multiple organ involvement had higher serum IgG and IgG4 levels than those with single organ involvement. Those with IgG4-related kidney disease (IgG4-RKD) had worse renal function. The incidence of peripheral blood eosinophilia and hypocomplementemia was higher in patients with renal involvement than in those without. Glucocorticoids-based therapy was most commonly used. (79.8%). Thirty-nine (41.5%) achieved complete remission. Eighteen (19.1%) relapsed after response to treatment. Eight (61.5%) of 13 patients with IgG4-RKD experienced improvement in renal function after treatment. None of the patients died during the follow-up period.

Conclusions: Kidney or other organ involvement is not significantly associated with clinical outcomes. Since IgG4-RD has different clinical features, it should be accurately diagnosed. Therefore, all physicians must actively diagnose and treat the condition.

Figure 1. Distribution of organs involved.

Figure 2. Treatment response.
Evaluation of Changes in Renal Microperfusion in Hyperuricemic-Induced Kidney Injury by Contrast-Enhanced Ultrasound Imaging

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Background: The diagnostic tools for early detection of renal injury caused by hyperuricemia are particularly lacking. Our study investigated the application of contrast-enhanced ultrasound (CEUS) in both hyperuricemic nephropathy (HN) rats and patients with hyperuricemia induced kidney injury.

Methods: Animal study was performed in hyperuricemic rat induced by feeding with a mixture of adenine and potassium oxonate for 4 weeks. In addition, 10 healthy volunteers and 40 patients with hyperuricemia induced kidney injury from CKD 1 to 4 stage were enrolled. CEUS was performed and low acoustic power contrast-specific imaging was used for quantitative analysis. Time-intensity curves (TICs) and quantitative indexes were created by Qlab software.

Results: In HN rat model generated by CEUS technique, a significant decline in renal cortical perfusion as reflected by lower Peak Intensity (PI) value (25.43±1.1 vs. 37.9±1.75db) and longer time to reach peak (TTP) intensity (34.5±0.9 vs. 85.8±1.6s) was found when compared to controls rats one week after administration of adenine and potassium oxonate, with more pronounced decline in HN rats. In patients with hyperuricemia induced kidney injury, the PI and TTP values also showed a decrease. The assessment of PI was well correlated with the serum KIM-1 level as well as the fibrosis scores in hyperuricemic rats from mild to advanced disease stage. Clinically, an early decline in PI of renal cortical perfusion was found in CKD stage 1 patients with hyperuricemia induced kidney injury as compared to the control group (61.4±52.5 vs. 65.8±10.1db), which became progressively less visible in patients with more severe kidney injury in these patients of CKD 4 stage (40.9±13.36 db). An early increase of TTP could also be detected in HN patients with CKD 1 stage as compared to normal control (15.1±2.75 vs. 14.3±2.5s), which became the most pronounced in these patients of CKD 4 stage (67.32±2.93s). In addition, Peak value measured by CEUS was correlated with renal function in patients with hyperuricemia induced kidney injury.

Conclusions: CEUS is able to detect the renal perfusion in a dynamic way. Renal perfusion measured by CEUS correlates with the renal functional impairment and tubulointerstitial fibrosis, suggesting a sensitive, reliable and non-invasive method that could be applied in the diagnosis of hyperuricemia induced kidney injury in clinical practice.

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The Effect of Kidney Function on Reference Intervals of Serum-Free Light Chains and Free Light Chain Kappa/Lambda Ratio

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Background: Current reference intervals for FLC and FLC ratio are inaccurate for patients with decreased kidney function. We propose new reference intervals for FLC and FLC ratio for use in patients with chronic kidney disease.

Methods: Current reference intervals for kappa, lambda, and FLC ratio depending on kidney function were previously published for serum free light chain (FLC) ratio (0.37–3.10) but does not take into account the degree of kidney failure. The aim of this study was to establish a kidney reference interval for FLC and validate the current and propose new kidney reference interval for FLC ratio.

Results: A total of 80,759 participants of the Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) study were included. Participants were screened with serum FLC (FREELITE) measurements and serum protein electrophoresis (SPEP) and immunofixation (IFE). Serum creatinine (SCR) value closest to the screening was used to calculate eGFR. Participants with M-protein, eGFR < 59 mL/min/1.73 m², missing SCR measurement or > 1 year from the iStopMM screening were excluded. A nonparametric evaluation of changes in renal microperfusion in hyperuricemic-Jam Soc Nephrol 32: 2021

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Molecular Stratification of CKD

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Background: Current classification of chronic kidney disease (CKD) into stages based on the indirect measures of kidney functional state, estimated glomerular filtration rate and albuminuria, is agnostic to the heterogeneity of underlying etiologies, histopathology, and molecular processes. We used genome-wide transcriptionomics from patients with kidney biopsies, including patients undergoing kidney biological processes, to stratify patients from three independent CKD cohorts.

Methods: Self-Organizing Maps (SOM), an artificial neural network machine-learning algorithm, assembled CKD patients into four novel subgroups, molecular categories, based on the similarity of their kidney transcriptionomics profiles.

Results: The unbiased, molecular categories were present across CKD stages and histopathological diagnoses, highlighting heterogeneity of conventional clinical subgroups at the molecular level. CKD molecular categories were distinct in terms of biological pathways, transcriptional regulation and associated kidney cell types, indicating that the molecular categorization is founded on biologically meaningful mechanisms. Importantly, our results revealed that not all biological pathways are equally activated in all patients; instead, different pathways could be more dominant in different subgroups and thereby differentially influence disease progression and outcomes.

Conclusions: This first kidney-centric unbiased categorization of CKD paves the way to an integrated clinical, morphological and molecular diagnosis. This is a key step towards enabling precision medicine for this heterogeneous condition with the potential to unlock biological understandings, clinical management, and drug development, as well as establish a roadmap for molecular reclassification of CKD and other complex diseases.

Funding: Commercial Support - This work was done as part of Renal Precompetitive Consortium (RPC2) collaboration (Tomilo et al, Drug Discov Today 2018) and was jointly funded by the participating members: AstraZeneca, Eli Lilly, NovoNordisk, Gilead, Janssen.

Determinants of Serum β2-Microglobulin and β-Trace Protein in South Asians

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Background: β2-Microglobulin (B2M) and β-trace protein (BTP) are being considered as a tool for use with creatinine and cystatin C to improve the GFR estimation (Inker, AKID 2020). In a Pakistani population, we showed that B2M and BTP did not improve the performance of eGFRs and eGFRcys-cys (Wang, Kidney Week 2021). We aimed to evaluate non-GFR determinants of B2M and BTP in a general population in Pakistan.

Methods: We used linear regression models to assess associations between possible determinants and log-transformed levels of B2M and BTP adjusting for measured GFR among 557 participants (≥40 years) from Pakistan. The strength of significant associations was defined as strong, intermediate, or weak if the absolute percent difference in B2M or BTP values was >10%, 5%-10% and <5%, respectively. R² was calculated in a model including all results.

Results: Non-GFR determinants with intermediate and strong associations with higher BTP included male sex, history of heart disease, and lower waist circumference. Non-GFR determinants of higher B2M included males, higher total body fat, and lower serum albumin. As shown in Table below, the non-GFR determinants assessed in our study along with measured GFR could explain 64.2% and 78.2% variance of BTP and B2M, respectively.
Conclusions: Factors associated with non-GFR determinants of BTP and B2M differ from those of cystatin C and creatinine. These and unidentified factors limit their usefulness in improving eGFR among South Asians.

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Table. Determinants and log-transformed filtration markers (N=557).

Table. The performances of GFR estimating equations in comparison with measured GFR (N=557).

PO2432

Rare Variant Analyses in 171,172 UK Biobank Participants Reveals Novel Genetic Associations with Renal Function and Kidney Diseases

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Background: GWASs have identified hundreds of common genetic variants associated with chronic kidney disease (CKD), but the burden of rare loss-of-function (LoF) or pathogenic/likely pathogenic (P/LP) variants has not been systematically examined.

Methods: We tested gene-based and variant-level association for 5 renal biomarkers (GFR [GFR Estimation Rate estimated from serum creatinine and/or cystatin-C, Blood Urea Nitrogen, Urine Albumin-to-Creatinine Ratio]) measured at enrollment and kidney-related diseases (e.g. End-Stage Renal Disease and stage/4 CKD, CKD defined by biomarker and/or diagnosis from NH data, Cystic kidney disease and Renal calculus) in 171,172 UK Biobank participants of genetically assessed European ancestry and with whole exome sequencing (WES). For each trait, we fit a genome-wide regression model and tested for association using REGENIE V2.0, adjusting for age, sex, 10 ancestry PCs, assessment center, and BMI where appropriate. For gene-based analyses, we generated 15 models to collapse ClinVar-classified LoF, putative LoF and deleterious variant predicted by 16 in silico scores (SIFT, PolyPhen, BayesDel, etc.) from dbNSFP 4.1c.

Results: We identified 33 and 18 genes associated with a2 biomarkers and a1 kidney diseases across collapsing models (FDR<0.05), respectively. PKD1/2, COL4A3/4, CUBN, IFT140 were associated with both biomarkers and kidney diseases. Association analyses also highlighted genes including: COL4A1, CST3, LAMA2, LRP2, SLC22A2, SLC34A3, and S12B3. Variant-level analyses further informed impact on protein, e.g. the SLC22A2 association signal was mainly driven by a frameshift (rs177505) with lowering effects on GFR (p=1e-27, beta=-6.2, MAF=0.12%). The exome-wide variant analyses revealed 29 genes (e.g. UMOD) with variant associations (p<5e-8) with ≥3 biomarkers or ≥1 kidney diseases across collapsing models (FDR<0.05), respectively.

Conclusions: This large-scale study elucidates the genetic landscape of kidney diseases. Our findings validate established genes and reveal novel genetic associations with renal function and kidney diseases.

Funding: Commercial Support - Janssen R&D

PO2433

High Dietary Phosphate Intake Causes Inflammatory Tubular Injury and Fibrosis in Mice

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Background: Due to the increasing consumption of processed food, the dietary inorganic phosphate intake clearly exceeds the recommended daily allowance. Elevated phosphate levels are associated with a higher cardiovascular and all-cause mortality in the general population and accelerated progression of chronic kidney disease (CKD). It is under investigation whether chronic phosphate load represents a renal health risk in the absence of CKD.

Methods: Male C57BL/6 mice were fed with a 2% high phosphate diet (HPD) or respective 0.8% phosphate diet (NPD) for six months. We collected blood, urine and kidneys to investigate phosphate metabolism, kidney function, tissue alterations and inflammation.

Results: Six months HPD significantly increased plasma levels of the phosphaturic hormone fibroblast growth factor (FGF) 23 resulting in enhanced phosphaturia and elevated serum phosphate level. HPD in mice caused albuminuria and increased plasma creatinine levels. Histological analyses revealed that mice on HPD developed proximal tubular injury characterized by loss of cell polarity and brush border membranes, flattened epithelial cells, severe interstitial inflammation, and tubular atrophy.

Funding: "Hannover Medical School Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover, Germany; "Hannover Medical School Institute of Pathology, Hannover, Germany; "Hannover Medical School Department of Nephrology and Hypertension, Hannover, Germany.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
epithelia, increased proliferation, mononuclear interstitial infiltration and fibrosis. The kidney damage imaging in the kidneys was accompanied by increased renal expression of the kidney injury marker Kim-1 and Ngal mice. Kim-1 accumulated in regions of tubular lesions. Flow cytometry analysis demonstrated that the HD patients contained LysC62 monocyties in the spleen and concurrently, enhanced accumulation of F4/80 macrophages and dendritic cells in the kidney. Histological analyses proved accumulation of F4/80 macrophages and CD3+ T-cells in areas of tubular injury that associated with increased renal expression of chemotaxis and growth factors for monocytes and macrophages Cer1, Csf1 and Il34 in HD patients. Finally, HD caused renal fibrosis associated with increased cytokines expression.

Conclusions: Chronic high phosphate load impairs kidney function by causing a strong inflammatory response and proximal tubular injury in healthy mice. Our results indicate chronic high phosphate intake might be a renal health risk not only for CKD patients but also for the general population.

PO2434
Apatelatone Downregulates Fibrotic, Inflammatory and Calcific Processes in Renal Mesangial Cells: Mechanism for Reduced Cardiac Injury

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Background: Major adverse cardiac events (MACE) are prevalent in patients with chronic kidney disease (CKD). Apatelatone inhibits BET proteins, which regulate expression of genes involved in fibrosis, inflammation & calcification. In the phase 3 BETonMACE trial, apatelatone reduced MACE in patients with CKD (eGFR<60) implying favorable effects on the kidney-heart axis. Here we examine apatelatone’s impact on pathways of nephropathy in human renal mesangial cells (HRMCs).

Methods: HRMCs were stimulated with TGF-β1 or LPS + a 1-25µM apatelatone. Gene expression was measured by qPCR & RNA-seq. Smooth muscle actin (a-SMA) was examined by immunofluorescence & alkaline phosphatase (TNALP) activity in biochemical assays. RNA-seq from TGF-β1 stimulated HRMC was evaluated by GO and Ingenuity Pathway Analysis (IPA).

Results: In HRMCs, apatelatone suppressed TGF-β1 induced pro-fibrotic gene expression including (a) a-SMA, a fibrotic marker, by >90% p<0.001 & de novo a-SMA protein production (b) extracellular, an matrix metalloproteinase (ECM) component, by 44% p<0.001 (c) NOX4, promoting reactive oxygen species (ROS) production, by >90% p<0.001 (d) TNALP promoting calcification, by 96% & TNALP activity by 96% p<0.001. Apatelatone opposed LPS induced inflammatory gene expression: IL6 by 94%, IL1B by 95% & PTGS2 (COX2) by 94% p<0.001. In GO, ECM gene sets were in the top 20 affected by apatelatone, indicating reduced fibrosis. IPA predicted inhibition of NFKB as a downstream mediator & discovery of NFKB complex to suppress inflammation, and activation of glucose utilization & tolerance of ROS production pathways, such as Oxidative Phosphorylation (z-score 5.7 p<0.001 at 25µM; z-score 3.5 p<0.005 at 5µM) and NRF2-Mediated Oxidative Stress Response (z score 2.3 p<0.001 at 25µM; z-score 1.6 p<0.001 at 5µM).

Conclusions: Apatelatone downregulates responses to TGF-β1 or LPS that promote fibrosis, inflammation & calcification in HRMCs. Changes in energy metabolism pathways predict apatelatone enables HRMC to cope with elevated glucose. Our results provide mechanistic insight into reduced MACE in CKD patients receiving apatelatone in the BETonMACE trial, & predict efficacy in the upcoming phase 3 BETonMACE2 trial.

Funding: Commercial Support - Resverlogix Corp.

PO2435
Characterization of Nano-Sized Silica in Sugarcane Ash and Its Potential Role in the Pathogenesis of CKD of an Unknown Etiology

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Background: Sugarcane burning by farmers in developing countries is hypothesized to contribute to an endemic kidney pathology called chronic kidney disease of an unknown etiology (CKDu). Further, elemental analysis revealed the sugarcane ash contained high levels of silica and iron. We hypothesized that burning of sugarcane generates nano-sized particles that are easily inhaled and translocated to the kidney thereby contributing to CKDu in sugarcane workers.

Methods: To determine if nano-sized particles are present in sugarcane ash, we utilized single particle inductively coupled plasma mass spectrometry (ICP-MS) and dynamic light scattering (DLS). To determine the effects of SINPs on the kidney, we used a human proximal convoluted tubule cell line (HK-2) to recapitulate the nephron’s exposure to sugarcane ash, desilicated ash, sugarcane ash derived SINPs, and pristine 200 mM SINPs at 0.25, 2.5, and 25 µM.

Results: Using single particle ICP-MS, we identified silica nanoparticles (SINPs) within digested sugarcane ash which ranged in size from 190-212 nm. DLS analysis of digested ash confirmed the presence of nanoparticles with a hydrodynamic diameter of ~110 nm. Although no desilicated ash was detected directly by HK-2, cells at 6 hours at any dose. SINPs are taken up leading to significant production of reactive oxygen species and mitochondrial superoxide within the first hour of exposure at all doses.

Conclusions: This indicates the presence of silica nanoparticles from sugarcane ash in HK-2. In less than 6 hours, the HK-2 cells exposed to sugarcane ash and epithelial mesenchymal transition occurring which will lead to a CKDu phenotype and disease pathogenesis.

Funding: NIDDK Support

PO2436
Release of ATP from Renal Tubular Epithelial Cells via Connexin 43 Deteriorates Renal Fibrosis After Unilateral Ureteral Obstruction

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Background: As a kind of DAMPs (Danger associated molecular patterns), ATP is released after stress or injury through ATP-permeable channels, most likely to be connexin hemichannels (Cx43) and P2 receptors. However, its role on renal injury and the following fibrosis has not been examined.

Methods: We analyzed renal samples from patients with obstructive nephropathy and applied unilateral ureteral obstruction (UUO) to induce renal fibrosis in mice. Cx43-KSP mice were generated to deplete the Cx43 gene of renal tubular epithelial cells (TECs).

Results: Through transcriptomics, metabolomics, and single-cell sequencing multi-omics analysis, the relationship among Cx43, ATP, and macrophage in renal fibrosis was explored.

Conclusions: Cx43 hemichannel mediates the outflow of ATP in TECs inducing macrophage proinflammatory response, which subsequently secretes CXCL10 facilitating activation and renal fibrosis.

Funding: National Natural Science Foundation of China.

PO2437
Single-Nucleus RNA-sequencing Analysis Elucidates Intercellular Interactions Between Inflammatory Parenchymal Cells and Immune Cells in the Kidneys with Tertiary Lymphoid Tissues

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Background: After acute kidney injury (AKI), elderly patients sometimes fail to recover and develop chronic kidney disease (CKD). We previously demonstrated that tertiary lymphoid tissues (TLTs) are formed in aged kidneys after AKI, resulting in prolonged inflammation and impaired regeneration, leading to CKD. However, the relationship of TLT formation in aged kidneys remains unknown.

Methods: Single nucleus RNA-sequencing (snRNA-seq) for three aged murine kidneys 30 days after ischemic reperfusion injury (IRI) as well as an aged kidney after sham operation was performed using the 10X platform. Computational analysis including unadjusted analysis, ligand-receptor analysis, and pseudotime trajectory analysis were performed. Gene expression was validated by immunostaining and high sensitivity in situ hybridization.

Results: SnRNA-seq generated 15968 and 7485 nuclei transcripts from IRI kidneys and a sham kidney, respectively, and demonstrated heterogeneous cell populations including parenchymal cells and immune cells in IRI kidneys with TLTs. We identified a subset of proinflammatory proximal tubules with sustained injury in IRI kidneys with TLTs, and confirmed that some of them surrounded TLTs. Ligand-receptor analysis suggested that the proinflammatory proximal tubules interacted with immune cells and fibroblasts. We also identified subsets of profibrotic fibroblasts and proinflammatory fibroblasts, and validated that the latter population was TLT-associated fibroblasts. Pseudotime trajectory analysis of fibroblasts showed that these two types of fibroblasts acquired distinct transcription factors and gene expression patterns along differentiation into distinct populations. Ligand-receptor analysis suggested that proinflammatory fibroblasts possibly contribute to survival and proliferation of B cells through BAFF production in TLT formation.

Conclusions: SnRNA-seq elucidated proinflammatory populations both in proximal tubules and fibroblasts in aged injured kidneys. Various intercellular interactions between the proinflammatory parenchymal cells and immune cells might contribute to TLT formation and these interactions have the potential to be promising therapeutic targets for AKI to CKD transition in the elderly.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
NGAL Is Necessary for Antigen-Presenting Cells Recruitment and Proteinuria in the Mouse Kidney with Ureteral Obstruction
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Background: Elevated levels of proteinuria are present in patients with chronic kidney disease (CKD) who are undergoing to UUO and to Sham surgery (Control) during 14 days (n=8). Creatinine and proteinuria were measured from pelvis urine of obstructed kidney. DCs (MHC-II+/CD11c+/CD80+/CD86+ for M1 phenotype) and M0 for M2 phenotype) recruitment were measured by flow cytometry. Additionally, WT-M0 were stimulated with albumin (10mg/ml, 24 h) and M1 genes evaluated by real-time PCR.

Results: We observed that the increased protein/creatinine ratio in the obstructed kidney of UUO WT mice was reduced in NGAL-KO mice (24.4±9.0 vs. 12.2±5.6, p<0.001). Flow cytometry simulation with albumin on macrophages from WT mice increased the mRNA levels of pro-inflammatory M1 markers (IL-12b, IL-23a, TNF-α±9.0 vs. 12.2±5.6, p<0.001). We did not observe changes in the M2 profile. Finally, we observed an early increase in the recruitment of DCs and M1 macrophages in WT UUO (MØp<0.001). We did not observe changes in the M2 profile. In vitro cytokine production, migration and endothelial adhesion assays were performed using ex vivo cells.

Results: NGAL-KO mice were higher in higher in CKD compared to PC (3.0±10 vs. 1.9±10, p<0.001). Following LPS stimulation in vivo CKD patients produced markedly higher amounts of TNF-α (p<0.001) and IL-1β (p<0.001) than other monocyte subpopulations. LPS-stimulated cytokine levels of human-CD14+ and human-CD14- monocytes in human-CD14+ and human-CD14- monocytes in human-CD14+ and human-CD14- monocytes is not different.

Conclusions: NGAL mediates the recruitment of monocytes and DCs in CKD. Supported by Fondecyt #1201251 and #3201016: Funding: Government Support - Non-U.S.

Role of Mast Cells in the Progression of Peritoneal Fibrosis in Rats with Chronic Renal Failure
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Background: Mast cells, that are originally derived from hematopoietic stem cells, secrete inflammatory cytokines besides their exocytotic release of chemical mediators. Recent studies also demonstrated that mast cells synthesize fibroblast-activating factors in chronic inflammatory diseases, thereby facilitating the progression of organ fibrosis.

Methods: Using rat models with chronic renal disease (CRM) induced by 5/6 nephrectomy, the histological and features of peritumoral fibrosis were examined. We also treated the CRM rats with tranilast, a mast cell stabilizer, to reveal the involvement of mast cells in the progression of peritoneal fibrosis.

Results: In fibrotic areas of CRF rat peritoneum, mast cells proliferated and phenotype, functional assays and serum isolation. Intracellular cytokine production, migration and endothelial adhesion assays were performed using ex vivo cells.

Results: Iron therapy improved anemia and mitigated kidney function decline in CKD mice, as indicated by serum creatinine improvement. Kidney iron was less severe in mice treated with iron compared to untreated mice in both the adenine and UO-modified diet. Intraperitoneal injection of iron dextran (0.5 g/kg body weight) was well tolerated and provided appropriate iron levels. While macrophage surface markers MHCII, CD86, and CD206 were altered by iron therapy, they did not follow the classical M1/M2 dichotomy. However, expression of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β by monocyte and macrophage populations was reduced in CKD mice treated with iron compared to untreated CKD mice.

Conclusions: Chronic parenteral administration of iron mitigated kidney fibrosis in two different mouse models, which, at least in part, was likely mediated by iron-induced kidney macrophage skewing towards an anti-inflammatory phenotype and reduced recruitment of pro-inflammatory cells into the kidney. Funding: NIDDK Support

Loss of Macrophage Mitofusin 2 but Not Mitofusin 1 Suppresses Mitochondrial Biogenesis and Promotes Kidney Fibrosis
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Background: Mitochondrial biogenesis, dynamics (fusion/fission) and mitochondria exert critical roles in maintaining mitochondrial function and protect against oxidative stress. Macrophages are well-known to aggravate kidney injury-induced inflammation and fibrosis in the pathogenesis of chronic kidney disease (CKD). We studied the effects of mitochondrial mitofusins: Mfn1 and/or Mfn2 deficiency on mitochondrial biogenesis during CKD.

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Underline represents presenting author.
Methods: Myeloid-specific Mfn1 (Mfn1fl/fl, LysMcCre−/−), Mfn2 (Mfn2fl/fl, LysMcCre−/−), and knockout (DKO) mice and corresponding controls were fed with control (C1) or adriamycin (AD) for 28 days. Kidneys, kidney macrophages, bone marrow-derived macrophages (BMDM) were analyzed by western blot, flow cytometry, immunohistochemistry. Blood urea nitrogen (BUN), creatinine were measured.

Results: Myeloid-specific deletion of the ubiquitin editor A20 spontaneously activates DCs. However, the role of Flt3L-expressing classical DCs in the kidney is unknown. Our data suggests that MVP contributes to interstitial fibrosis. Inhibition of classical DCs may ameliorate autoimmune nephritis. The role of Flt3L-expressing classical DCs in the regulation of inflammatory CKD requires elucidation. We hypothesized that classical dendritic cells exacerbate kidney injury by promoting the activation of renal T cells.

Results: We developed nephroprotective nephritis (NTS) in flt3-deficient mice lacking DCs (DC KO, mice with spontaneous DC activation (CD11cCre A20fl/fl = DC ACT), and wild-type (WT) controls. After 14 days of NTS, kidney injury was assessed by histological analysis. Compared to WTs, DC ACT mice showed higher superoxide dismutase-2, mitochondrial fusion proteins: Mfn1, Mfn2, and OPA-1 decreased while fusion proteins: DRP-1 and phospho-DRP-1-Serine-616 increased in the kidneys after AD and BMDM after TGF-β1 treatment. Kidney macrophage superoxide levels increased after AD, but not in WT and Mfn1fl/fl mice. Wild-type and Mfn1fl/fl mice showed similar increases in collagen deposition in the kidney and worsening of kidney function after AD. BMDM from Mfn1fl/fl, LysMcCre−/− and DKO mice also showed similar expression of profibrotic macrophage marker, arginase-1 after TGF-β1 treatment. However, TGF-β1-treated Mfn1fl/fl, LysMcCre−/− and DKO BMDM and kidney macrophages displayed greater polarization towards profibrotic phenotype while lower expression of PGE-1α and decreased misfolding than Mfn1fl/fl, LysMcCre−/− and wild-type macrophages.

Conclusions: Macrophage-specific deficiency of Mfn2 but not Mfn1 causes impairments in mitochondrial biogenesis and misfolding, thereby promoting polarization towards profibrotic macrophage phenotype and kidney fibrosis.

Funding: Other NIH Support - NHLBI

PO2443

F4/80hi Resident Macrophages Contribute to Cisplatin-Induced Kidney Fibrosis and M2 Polarization in C57BL/6 Mice

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Background: Cisplatin is a mainstay in the treatment of many solid-organ cancers. Its therapeutic benefits, however, are hindered by dose-limiting nephrotoxicity. Cisplatin causes acute kidney injury (AKI) in 30% of patients. Development of AKI puts patients at risk for development of fibrosis and chronic kidney disease (CKD). Cisplatin-induced kidney fibrosis can be modeled in rodents using repeated, low doses of cisplatin once a week for four weeks. Understanding the mechanisms that promote fibrosis in this model could improve long-term care of cancer patients who receive cisplatin. Macrophages are known to respond to kidney injury and correlate with progression of fibrosis in CKD patients, indicating they may be key regulators of fibrosis development following kidney insults. We hypothesize that chronic macrophage activity promotes cisplatin-induced kidney fibrosis.

Methods: In this study, we depleted populations of F4/80hi resident macrophages and F4/80hi infiltrating macrophages in C57BL/6 mice using either clodronate encapsulated liposomes or CCR2 genetic knockout, respectively. In parallel with this macrophage depletion, mice were given 4 weekly doses of 9 mg/kg cisplatin. After euthanization, we evaluated kidney function, injury, and fibrosis development.

Results: Our data suggests that F4/80hi resident macrophage depletion ameliorates development of cisplatin-induced fibrosis, as measured by statistically significant decreased collagen deposition and myofibroblast accumulation. In contrast, CCR2 knockout mice, which were deficient in infiltrating macrophage depletion, did not alter pathological outcomes after cisplatin treatment. Additionally, deletion of resident macrophages, but not infiltrating macrophages, decreased accumulation of CD206+ M2 macrophages in cisplatin treated kidneys.

Conclusions: Taken together, these data suggest that F4/80hi resident macrophages may be key drivers in the development of cisplatin-induced kidney fibrosis and the primary source of M2 macrophages in the kidney. Therefore, kidney resident macrophages represent a possible target for preventing long-term kidney damage associated with cisplatin treatment.

Funding: NIDDK Support

PO2446

Lactate Dehydrogenase A Influences Pro-Inflammatory Polarization of Murine Bone Marrow-Derived Macrophages

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Background: Excessive inflammation is a major underlying pathophysiologic factor in the progression of chronic kidney disease (CKD). Infiltration of pro-inflammatory macrophages can provoke such inflammatory responses. Macrophages undergo transcriptional and metabolic reprogramming and rely heavily on glycolysis. Lactate Dehydrogenase A (LDHA) is a key enzyme involved in the glycolytic switch which catalyzes the conversion of pyruvate to lactate and regenerates NAD+ from NADH. Utilizing LDHA deletion, we investigated the effect of suppression of the glycolytic switch in macrophages in vitro and in vivo.

Methods: Mature bone marrow-derived macrophages (BMDMs) from wild-type and LDHA knockout mice (KO) mice were cultured and then polarized for 24 hours using IFN-γ, Bulk RNA seq (transcriptional) and LC-MS/MS (metabolomic) experiments were performed. For in vivo studies, wild-type littermate and myeloid deficient LDHA KO were treated with aristolochic acid A1 (AA) for 6 weeks as a model of CKD.

Results: LDHA-deficient BMDMs showed diminished pro-inflammatory profile in vitro and decreased renal fibrosis in vivo. These results highlight LDHA’s role as a novel candidate target for manipulation in immunometabolism and may have a significant impact on approach to CKD.

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

PO2445

Major Vault Protein Promotes Macrophage-to-Myofibroblast Transition and Tubulointerstitial Fibrosis in a Murine Model of CKD

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Background: Chronic kidney disease (CKD) is characterized by progressive interstitial fibrosis and tubular atrophy, and inflammatory cell infiltration. We found that major vault protein (MVP), a key component of the vault complex, contributed to macrophage matrix protein deposition in an adriamycin-induced murine CKD model. We continued to investigate whether MVP contributes to interstitial fibrosis.

Methods: MVP was induced in wild-type (WT) and knockout (KO) mice by feeding with casein-based chow containing 0.2% ademe for 8 weeks, and mice were sacrificed and renal cortical tissue harvested for qPCR, immunohistochemistry and flow cytometry analysis. Mice fed casein-based chow served as controls.

Results: MVP WT mice with CKD showed increased MVP mRNA compared to control WT mice. In MVP WT mice with CKD there was increased macrophage infiltration in the tubulo-interstitium that co-localized with collagen I, fibronectin and smooth muscle actin, suggesting macrophage-to-myofibroblast transition. Flow cytometric data showed increased CD45+ cells and F4/80hi /CD11b+ macrophages in MVP WT mice with CKD. MVP KO mice with CKD showed reduced infiltration of macrophages in the tubulo-interstitium, with lower transition to myofibroblasts (P<0.01; and there was decreased MCP-1, MCP-1 receptor and TNF-a mRNA expression, with better preservation of normal renal histology.

Conclusions: The findings suggest that MVP may contribute to the pathogenesis of CKD by promoting macrophage infiltration and their transition to myofibroblasts.

Funding: Government Support - Non-U.S.

PO2446

Classical Dendritic Cells Mediate Nephrotoxic Serum Nephritis by Activating T Cells

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Background: Glomerulonephritis is a prominent cause of chronic kidney disease (CKD) and features robust chronic inflammation. Following an inflammatory insult, myeloid cells infiltrate the kidney and drive CKD progression. Flt3L-expressing classical dendritic cells (DCs) are the most potent antigen-presenting cells, and heterogeneous deletion of the ubiquitin editor A20 spontaneously activates DCs. However, the role of Flt3L-expressing classical DCs in the regulation of inflammatory CKD requires elucidation. We hypothesized that classical dendritic cells exacerbate kidney injury by promoting the activation of renal T cells.

Methods: We induced nephrotoxic serum nephritis (NTS) in flt3-deficient mice lacking DCs (DC KO, mice with spontaneous DC activation (CD11cCre A20fl/fl = DC ACT), and wild-type (WT) controls. After 14 days of NTS, kidney injury was assessed by histological scoring and ACRs. In addition, mRNA levels of renal injury biomarkers were measured by qPCR. NTS BlcA mice and wild-type (WT) controls. In MVP WT mice with CKD there was reduced mRNA expression of inflammatory cytokines.

Conclusions: The findings suggest that MVP may contribute to the pathogenesis of CKD by promoting macrophage infiltration and their transition to myofibroblasts.

Funding: Government Support - Non-U.S.
Targeting Innate Immune-Polyamine Axis Prevents CKD-Associated Cardiac Hypertrophy
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Background: It is well recognized in clinic that patients with chronic kidney disease (CKD) have a higher risk for developing cardiovascular diseases including cardiac hypertrophy. However, the pathogenetic mechanisms remain poorly understood.

Methods: The hypertrophic phenotype changes and metabolic characteristics of neonatal rat cardiomyocytes were studied after incubation with serum from 5 stage CKD patients, as well as myocardium from mice with or without CKD, accompanied by bulk RNA-seq analysis. The role and mechanism of CKD in inducing cardiac hypertrophy were evaluated in vivo and ex vivo, and confirming in targeted gene knockout and cardiomyocyte-specific knockdown mice.

Results: Here, we show that adult cardiomyocytes are characterized by restrained polyamine metabolism, while CKD activates polyamine metabolism especially ornithine decarboxylase (ODC1)-putrescine metabolic axis in cardiomyocytes. Then, we reveal that nuclear factor kappa B (NFκB)-driven hypertrophic program, rather than a pathogenic factor for cardiac hypertrophy. Furthermore, mitochondrial oxidative damage is a prominent feature of cardiomyocytes under CKD milieu. The damaged mitochondria release mitochondrial DNA into the cytosol and stimulates the innate immune cyclic GMP-AMP synthase-stimulator of innate immune (cGAS-STING) pathway in cardiomyocytes, which subsequently activates NFκB. Therefore, myocardial cGAS-STING-NFκB-driven hypertrophic program plays a critical role in CKD-associated cardiac hypertrophy through immune surveillance of mitochondrial DNA.

Conclusions: Our study uncovers a previously unrecognized role of innate immune-polyamine axis in CKD-associated cardiac hypertrophy. Targeting innate immune-polyamine axis may represent a promising strategy to prevent and treat CKD-associated cardiac hypertrophy.

Funding: Government Support - Non-U.S.

The Active Ingredient in the Nuphar lutea Plant, 6,6-Dihydroxythiobinupharidine (DTBN), Ameliorates Kidney Fibrosis, Inflammation, and Anemia in a Mouse Model of CKD
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Background: EPO resistance and iron deficiency in CKD-related anemia are associated with an increase in inflammatory cytokines associated with the innate immune response, such as IL-6, IL-1, and TNF-α. Recently (Bandach et al, Sci Reports 2021) we reported that kidney fibrosis and anemia of CKD can be worsened or relieved when IL-1α and IL-6 are deleted or inhibited, respectively. The Water lily (Nuphar lutea) plant has been widely used as a traditional remedy for the treatment of rheumatism, scar, pain, and more. Gopas, Golan-Goldhirsh et al (Cancer Biology Therapy 2009) extracted an active ingredient from the family of nupharidines: 6,6-Dihydroxythiobinupharidine (DTBN) which showed anti-inflammatory properties, mainly through the inhibition of NFκB. The purpose of this study was to test the effects of DTBN in a mouse model of CKD-associated anemia.

Methods: 8 weeks old male C57BL/6 mice were divided into 3 groups: Control, CKD (induced by adenine diet) and CKD-DTBN. CKD groups were injected with saline-DMSO or 30 µg DTBN, every two days and sacrificed after 3 weeks from dietary intervention.

Results: Serum urea and kidney TGFβ mRNA were significantly decreased in CKD-DTBN Vs CKD. Kidney histology in CKD mice showed macrophage infiltration and renal fibrosis, which was ameliorated in CKD-DTBN. A significant improvement in inflammation indices (blood lymphocytes, kidney and liver IL-6 and p-STAT3, liver CRP), as well as kidney immunoreactive NFκB and F4/80, which were increased in CKD, were decreased in CKD-DTBN. CKD anemia indices (hemoglobin, hematocrit, and RBC count) significantly improved in CKD-DTBN. Kidney HIF-2α and EPO mRNA were significantly decreased in both uremic groups, but was unchanged in CKD-DTBN Vs CKD. However, serum iron and transferrin saturation significantly increased in CKD-DTBN Vs CKD.

Conclusions: Uremic mice treated with DTBN show improvement in kidney fibrosis, inflammation and anemia indices. Thus, DTBN may be a novel therapeutic alternative for CKD and its complications.
**PO2451**

**Complement C5a Receptor in Macrophage-Mediated Renal Inflammation and Fibrosis in Lupus Nephritis**  

**Background:** Lupus nephritis (LN) is caused by autoimmune responses and is a significant driver of end-stage renal disease in systemic lupus erythematosus patients. Complement activation, pro-inflammatory cytokine production, and the influx of macrophages have all been implicated in LN pathogenesis. The anaphylatoxin complement 5α (C5a) receptor 1 (C5aR) is a major driver of the pro-inflammatory functions of complement activation. We examined C5aR’s expression in kidney in lupus nephritides and investigated its role in controlling pro-fibrotic functions of macrophages.

**Methods:** C5aR expression, infiltrating immune cells, and fibrosis were examined by immunohistochemistry in LN patient kidneys biopsies. M1 and M2 macrophages derived from human peripheral blood monocytes were used in in vitro assays to examine the effect of C5a stimulation and avacopan, a specific C5aR inhibitor, on the secretion of cytokines and other factors.

**Results:** In LN kidney biopsies, large numbers of macrophages, identified by CD68 staining, were observed in areas with severe fibrosis, and expressed C5aR. In addition, C5aR was detected on distal tubules in biopsies of both normal and lupus nephritis kidneys. C5a increased the production of inflammatory cytokines TNFa and IL-6 from both M1 and M2 macrophages in vitro. Chemokines (MCP-3, MIP-1α, MIP-1β and MIP-3α), matrix metalloproteinases (MMP3 and MMP8), and pro-fibrotic growth factors (fibroblast activation protein, platelet-derived growth factor-α(PP)-AA) were strongly increased in M2 macrophages with C5a stimulation, and these increases were blocked by the C5aR inhibitor avacopan.

**Conclusions:** C5aR activation induced macrophage secretion of factors that are known to contribute to inflammation, fibroblast activation and tissue fibrosis, and thus may contribute to LN disease progression. Inhibiting C5aR activity with avacopan blocks these pathological changes, and may provide therapeutic benefit to LN patients.

**PO2452**

**Remdesivir Inhibits Tubulointerstitial Fibrosis in Obstructed Kidneys**  
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**Background:** Kidney impairment is observed in patients with COVID-19. The effect of anti-COVID-19 agent remdesivir on kidneys is currently unknown. We aimed to determine the effect of remdesivir on renal fibrosis and its downstream mechanisms.

**Methods:** Remdesivir and its active nucleoside metabolite GS-441524 were used to treat TGF-β-stimulated renal fibroblasts (NRK-49F) and human renal epithelial (HK2) cells. Vehicle or remdesivir were given by intraperitoneal injection or renal injection through the left ureter in unilateral ureteral obstruction (UUO) mice. Serum and kidneys were harvested. The concentrations of remdesivir and GS-441524 were measured using LC-MS/MS. Renal and liver function were assessed. Renal fibrosis was evaluated by Masson’s trichrome staining and Western blotting.

**Results:** Remdesivir and GS-441524 inhibited the expression of fibrotic markers (fibronectin and ASMA) in NRK-49F and HK2 cells. Intraperitoneal injection or renal injection of remdesivir attenuated renal fibrosis in UUO kidneys. Renal and liver function were improved. Renal fibrosis in remdesivir treated UUO mice. Two remdesivir metabolites were detected after injection. Phosphorylation of Smad3 that was enhanced in cell and animal models for renal fibrosis was attenuated by remdesivir. In addition, the expression of Smad7, an anti-fibrotic factor, was increased after remdesivir treatment in vitro and in vivo.

**Conclusions:** Remdesivir inhibits renal fibrosis in obstructed kidneys.

**Funding:** Government Support - Non-U.S.

**PO2453**

**Heightened Innate Immune Response to COVID-19 Infection in CKD: Implications to Poorer Outcome During CKD**  
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**Background:** Meta-analyses reveal a significant association of chronic kidney disease (CKD) with severe COVID-19. The double stranded RNA virus SARS-CoV2 can evoke a damaging inflammatory response. To determine the mechanisms for the severity of the disease in patients with CKD, we studied an animal model of CKD exposed to polyinosinic-polycytidylic acid (poly(I:C), a synthetic analog of double-stranded RNA) to evoke a damaging inflammatory response. To understand the mechanism for the greater fibrosis in CKD, we used a 2-week poly(I:C) treatment and grown in serum-free medium supplemented with macrophage colony stimulation factor for 7 days to obtain bone marrow derived macrophages (BMDM). These cells were stimulated with 10 µg / ml poly(I:C), followed by measurement of proinflammatory cytokines. Single cell RNA sequencing was used to compare transcriptome between normal and CKD kidneys.

**Results:** CKD animals had elevated plasma creatinine (0.14 ± 0.02 mg/dl, n=8, control 0.09 ± 0.01 mg/dl, n=5, p=0.05) and elevated plasma levels kidney injury marker 1 (KIM-1; 133.6 ± 29.9 pg/ml, vs undetectable, n=5, p=0.05). Poly(I:C) treatment induced a greater body weight loss in CKD animals (9.9±2.9 %, n=8 vs control mice 6.8±2.0 %, n=5; p=0.005) and greater mortality of CKD mice (46% mortality within 3 weeks vs no mortality in control mice). BMDMs from CKD mice produced greater levels of IL-6 than control BMDC upon poly (I:C) stimulation at both the mRNA and protein levels. In addition, Single cell RNA sequencing revealed that there is 3-fold higher relative number of macrophages in CKD kidneys.

**Conclusions:** Our results show that CKD mice are more sensitive to foreign double strand RNA insult. BMDM isolated from cisplatin-induced CKD demonstrated a greater innate immune response during CKD. We propose that the inherent hyperinflammatory nature of CKD drives a greater innate immune response in this model of viral injury and may be responsible, at least partially, for the poor outcomes in CKD patients with COVID-19 infections.

**Funding:** NIDDK Support

**PO2454**

**Combined Soluble Epoxide Hydroxide Inhibition and Epoxyeicosatrienoic Acid Administration Attenuates the Renal Fibrogenesis Without Additivity or Synergy**  
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**Background:** Epoxyeicosatrienoic acids (ETEs) are arachidonic acid metabolites with biological effects, including anti-apoptotic, anti-inflammatory, and anti-fibrotic functions. Soluble epoxide hydroxide (sEH)-mediated hydrolysis of EETs to dihydroyeicosatrienoic acids (DHETs) attenuates their biological effects. Recent studies have demonstrated inhibition of sEH prevents renal tubulointerstitial fibrosis and inflammation in chronic kidney disease (CKD) model. Here, we demonstrated the role and underlying mechanism of EETs in unilateral ureteral obstruction (UUO)-induced renal fibrogenesis.

**Methods:** Eight-week-old male wild type (Ephx2−/−) and Ephx2−/− mice underwent sham or UUO surgical procedures and were treated with the combination of 11,12- and 14,15-EETs (15 µg/kg/day, respectively) using osmotic pump for 7 days following UUO surgery.

**Results:** EETs administration abolished tubulointerstitial fibrogenesis, as demonstrated by reduced fibroblast activation and collagen deposition after UUO. Furthermore, inflammatory response was prevented as demonstrated by decreased macrophage infiltration and expression of inflammatory cytokines (TGF-β, IL-1β and IL-6) in EETs-administered UUO kidneys. The genetic inhibition of sEH also mitigated UUO-induced renal inflammation and interstitial fibrogenesis. The combination of EET administration and sEH inhibition also attenuated inflammation and renal interstitial fibrogenesis after UUO, but no additive or synergic effect of combined sEH inhibition and EETs administration.

**Conclusions:** Taken together, our findings provide that the underlying mechanism of EETs in kidney fibrogenesis during obstructive nephropathy, suggesting EETs as a potential therapeutic target of kidney fibrosis progression.

**Funding:** NIDDK Support

**PO2455**

**EP1 Receptor Antagonism Mitigates Early and Late-Stage Renal Fibrosis**  
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**Background:** Renal fibrosis is a hallmark of Chronic Kidney Disease (CKD), which affects 10-16% of the world’s adult population. Yet current treatment strategies are ineffective in attenuating renal fibrogenesis. Therefore, we are in urgent need for new therapeutic strategies against renal fibrosis. The cyclooxygenase/prostaglandin (COX/PG) system plays a key role in renal fibrosis and holds great promise as a suitable therapeutic target. Here, we used a translational approach to evaluate the role of the PGE1, EP1 receptor in the pathogenesis of renal fibrosis in several models of kidney injury, including human (fibrotic) kidney slices.

**Methods:** The anti-fibrotic effect of SC-19220 - an EP1 receptor antagonist - was studied in Madin-Darby Canine Kidney (MDCK) cells, mice subjected to seven days of unilateral ureteral obstruction (UUO), and healthy and fibrotic human precision-cut kidney slices (PCKS). Progression of fibrosis was evaluated on gene and protein level using qPCR, Western blot and immunohistochemistry.

**Results:** Pharmacological inhibition of the EP1 receptor using SC-19220 reduced TGF-β-induced fibronectin (FN) expression, ERK1/2 phosphorylation and epithelial-to-mesenchymal transition in MDCK cells. Moreover, SC-19220 diminished fibrosis in UUO mice, measured by decreased protein expression of FN and α-smooth muscle actin (αSMA), and a reduction in collagen deposition. In addition, treatment of healthy human PCKS with SC-19220 reduced TGF-β-induced fibrogenesis as shown by decreased gene levels of collagen 1A1, FN and αSMA as well as reduced collagen deposition. Moreover, similar observations were made using fibrotic human PCKS.

**Conclusions:** This study highlights that the EP1 receptor is a promising target for preventing both the onset and late stage of renal fibrosis. Moreover, we provide strong evidence that the effect of SC-19220 may translate to clinical care since its effects were observed in UUO mice and human kidney slices.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**

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**749**
Selective Activation of the Prostaglandin E2-EP4 Receptor Can Slow or Reverse the Fibrotic Process in Human Kidney Slices

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Background: Chronic kidney disease (CKD) affects approximately 10% of the population, and renal fibrosis, i.e., excessive scar formation in the kidney, is one of the major pathological processes leading to end-stage renal disease (ESRD). Despite overwhelming efforts to find therapies to reduce renal fibrosis, current management strategies are ineffective at preventing disease progression in CKD patients. Activation of the prostaglandin E2-EP4 receptor has been shown to have renoprotective effects in cell and animal studies. However, translational studies using human kidney tissue are lacking.

Methods: In this project, we studied the anti-fibrotic effect of the selective EP4 receptor agonist Rivenprost using a translational model of renal fibrosis, namely human precision-cut kidney slices (PCKS). This model is ideal to study multicellular pathological processes, e.g., fibrosis, directly in human tissue, since cellular diversity and organ architecture is maintained in the slices. Macroscopically healthy renal tissue (n = 13) was obtained from tumor necrectomies, whereas fibrotic renal tissue (n = 6) was obtained from ESRD nephrectomies. Subsequently, PCKS were incubated with Rivenprost (75μM) to evaluate its anti-fibrotic effect directly in human tissue. Fibrogenesis was evaluated on a gene level using qPCR. Viability was assessed by ATP measurements using ELISA. Protein and histological analyses are ongoing.

Results: The expression of the EP4 receptor in PCKS was increased twofold after 48h of incubation with the pro-fibrotic cytokine TGFβ1, suggesting that the EP4 receptor might play a role in the fibrotic process. Treatment with Rivenprost mitigated TGFβ1-induced fibrogenesis in healthy tissue. Moreover, Rivenprost halted disease progression in fibrotic PCKS and appeared to partly reverse fibrosis, as illustrated by a reduction in the gene expression of α-smooth muscle actin, fibronectin and collagen I by at least 50% without affecting the viability of the human PCKS.

Conclusions: Selective stimulation of the PGE2-EP4 receptor can slow and reverse the fibrosis process directly in human renal tissue. These findings warrant further research into the clinical application of Rivenprost, or other EP4 receptor agonists, as a treatment for (established) renal fibrosis.

Mice with a Deficient Myeloid COX-2/EP4 Axis Developed More Severe Kidney Dysfunction in Response to a High-Fat Diet

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Background: Obesity leads to a state of chronic, low-grade inflammation that contributes to insulin resistance and type 2 diabetes as well as chronic kidney injury. Macrophages are major contributors to obesity-associated adipose inflammation and dysregulated metabolism. When fed a high fat diet (HFD), cyclooxygenase-2 (COX-2) expression increased in adipose tissue macrophages (ATMs). Mice with myeloid deletion of COX-2 or its EP4 receptors resulted in increased obesity after the HFD. The current studies investigated whether kidney dysfunction was exacerbated in mice with myeloid COX-2 or EP4 deletion fed a HFD.

Methods: once we developed myeloid COX-2-/- mice (CD11b-Cre; COX-2 f/f) and myeloid EP4-/- mice (CD11b-Cre; EP4 f/f). COX-2-/- mice and EP4-/- mice were used as corresponding WT controls. The mice were fed a HFD (36% fat accounting for 60% of calories) for 12 weeks.

Results: The HFD induced greater increases in body weight, fasting blood glucose, and plasma concentrations of insulin, free fatty acids, TNF-α, and leptin in the observed exacerbated kidney dysfunction are associated with dysregulated metabolism. When fed a high fat diet (HFD), cyclooxygenase-2 (COX-2) expression increased in adipose tissue macrophages (ATMs). Mice with myeloid deletion of COX-2 or EP4 receptors resulted in increased obesity after the HFD. The current studies investigated whether kidney dysfunction was exacerbated in mice with myeloid COX-2 or EP4 deletion fed a HFD.

Conclusions: These studies found that mice with myeloid cell deletion of COX-2 and EP4 are more sensitive to high fat diet-induced obesity and develop more severe kidney dysfunction and immune cell infiltration. The potential role of increased adipokines, insulin, free fatty acids, and leptin in the observed exacerbated kidney dysfunction are under investigation.

Funding: NIDDK Support, Veterans Affairs Support
Guainidinylated Apolipoprotein C3 (ApoC3) Causes Kidney and Vascular Injury

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Background: Cardiovascular diseases (CVD) and chronic kidney diseases (CKD) are highly prevalent in Western populations and account for a substantial proportion of mortality. We found that guainidinylated ApoC3 (gApoC3), a constituent of triglyceride-rich lipoproteins, induces alternative NLRP3 inflammasome activation in human monocytes and thus causes sterile inflammation. The aim of the present study was to screen gApoC3 for the presence of posttranslational modifications and to assess its relevance in vitro, in vivo, as well as in a prospective cohort of patients.

Methods: gApoC3 was subjected to proteomic analysis. The proinflammatory properties of gApoC3 were assessed in human monocytes and in humanized mice. Moreover, posttranslationally modified gApoC3 was quantified in a prospective cohort of 543 patients with various etiologies of CKD and linked to kidney and cardiovascular outcomes.

Results: We identified posttranslational guainidinylation of lysine residues of gApoC3 in patients after acute myocardial infarction and in patients with CKD. gApoC3 accumulates in kidneys and hearts after injury as determined by 2D-proteomic analyses. In human monocytes, guainidinylation enhanced the binding of gApoC3 to the cell surface and exerted substantially stronger pro-inflammatory effects as compared native ApoC3. In humanized mice, gApoC3 strongly induced kidney fibrosis and abolished the regeneration after vascular injury. In a prospective clinical trial of 543 patients, higher gApoC3 blood levels as determined by mass spectrometry were associated with increased mortality as well as cardiovascular and renal events during a long-term follow-up.

Conclusions: The present study provides evidence from preclinical models and a prospective clinical trial that gApoC3 plays an important role in the development of organ injury in patients with CKD, myocardial infarction and other clinical conditions. The clinical study represents one of the largest trials, in which the association of a specific PTM and clinically relevant outcomes was assessed. These findings highlight gApoC3 as a pathophysiologically relevant factor in the development of organ dysfunction.

PO2462

Key Role for EphB2 Receptor in Kidney Fibrosis

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Background: Eph- Ephrin receptor-ligand signaling has been implicated in the development of tissue fibrosis, though it has not been well defined in the kidney. Methods: We then firstly made use of male EphB2-knockout and littermate control mice (n=5/per group) to receive unilateral renal ischemia-reperfusion (IR) surgery for 35min. In addition, EphB2 signaling was further determined in varied kidney disease models, particularly in diabetic- or hypertension-induced kidney disease models and in the kidney biopsy tissue from IgA nephropathy with glomerulosclerosis and tubular fibrosis.

Results: We detected substantial upregulation of expression and phosphorylation of the EphB2 receptor tyrosine kinase in fibrotic kidney tissue obtained both from mice subjected to either the unilateral renal IR model at 14 days or type 2 diabetics or DOCA & Ang II-infused hypertension and in patients suffering from chronic kidney disease (CKD). Knockout mice lacking EphB2 expression exhibited a normal renal structure and function, indicating no major role for this receptor in kidney development or action. Although IR injury is well known to cause tissue damage, fibrosis, and renal dysfunction, we found that kidneys from EphB2 knockout mice showed much less renal tubular injury and retained a more preserved renal function. IR-injured kidneys from EphB2 knockout exhibited greatly reduced fibrosis and inflammation compared to injured wild-type (WT) littermates, and this correlated with a significant reduction in renal expression of pro-fibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition, myofibroblast activation, and apoptosis. A panel of 760 fibrosis-associated genes were further assessed, revealing that 506 genes in WT mouse kidney following IR injury changed their expression. However, 70.9% of these genes were back to or close to normal in expression when EphB2 was deleted.

Conclusions: These data indicate endogenous EphB2 expression and signaling are abnormally activated after kidney injury and subsequently contributes to the development of renal fibrosis via regulation of multiple pro-fibrotic pathways.

Funding: NIDDK Support

PO2461

Endothelial Function, Oxidative Stress, and Cognitive Performance in CKD

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Background: Cognitive impairment, common in patients with chronic kidney disease (CKD), can be explained at least partially by the high prevalence of cerebrovascular diseases in the population. Here, we hypothesized that endothelial dysfunction associates with reduced cognition in patients with CKD.

Methods: We conducted a cross-sectional study of 63 middle-aged/older adults with CKD stage 3b and 4. Cognitive function domains including executive function, memory, language, and processing speed were assessed via the NIH-Toolbox. Endothelial function of the brachial artery was assessed via flow-mediated dilation (FMD) using Doppler ultrasound. The influence of oxidative stress on FMD was determined by infusing ascorbic acid. Association between FMD and any of the cognitive domains. However, a greater response to ascorbic acid correlated with better age-adjusted memory performance independently of education (95% CI: 2.08: 0.51,3.65; p<0.05).

Results: The mean(SD) age, estimated glomerular filtration rate (eGFR), and FMD of the participants were 64(9), 34(11), and 2.6(1.4). Ascorbic acid increased FMD by 2.5±1.7 as compared to saline which increased FMD by 2.5±1.4. In A-CKD group, CCh-relaxation response was significantly improved compared to S-CKD, while L-NAME pre-incubation abolished the relaxation (Fig E-F).

Conclusions: Oxidative stress contributes to endothelial dysfunction in CKD and a greater response to ascorbic acid is associated with better memory performance. More studies are needed to understand the role of oxidative stress in cognitive impairment in patients with stage 3b/4 CKD.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

Table 1: NIH Toolbox Cognitive Domain Standard Scores

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Standard Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Function</td>
<td>95.95±2.1</td>
</tr>
<tr>
<td>Memory</td>
<td>96.5±4.6</td>
</tr>
<tr>
<td>Language</td>
<td>89.5±9.3</td>
</tr>
<tr>
<td>Processing speed</td>
<td>100.6±2.1</td>
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</tbody>
</table>

Normatively age-adjusted standard scores are presented. Standard scores have a mean of 100 and SD of 15.
PO2464

Apelin and FGF-23 as Biomarkers for Vascular Calcification in Type 2 Diabetic Patients with CKD
Rita S. Afonso, Ana Cabrita, Ana P. Silva. Centro Hospitalar do Algarve EPE, Faro, Portugal.

Background: Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients. CKD-Mineral and Bone Disorder occur from the earliest stages of estimated glomerular filtration rate (eGFR) loss and is associated with an increased risk of vascular calcification (VC), which is one of the strongest predictors of cardiovascular risk and mortality in patients with CKD. Apelin and FGF-23 have emerged as potential markers of VC. The main objective of this study is to evaluate the role of apelin and fibroblast growth factor 23 (FGF-23) in the development of VC in type 2 diabetic CKD patients.

Methods: Observational prospective study enrolling 150 type 2 diabetes mellitus patients with CKD. Sample characteristics were analyzed using descriptive statistics. Independent-samples t-test, Pearson’s correlation test and partial correlations were used to evaluate the association and correlation of several desmographic and clinical parameters with vascular calcification score (VCS). Univariate logistic regression and multivariate logistic regression were used to find out predictors of VC.

Results: Lower levels of apelin, 1,25-dihydroxycholecalciferol and eGFR were negatively associated with higher VCS and higher levels of phosphate, calcium x phosphate, parathyroid hormone, interleukin-6 and FGF-23 were positively associated with higher VCS. A negative correlation was found between VCS and apelin (r = -0.429, p<0.0001), and between apelin and FGF-23 (r = -0.483, p<0.0001), while a positive correlation was found between VCS and FGF-23 (r = 0.232, p=0.005). Variables significantly associated with VCS in univariate logistic regression analysis were used in multivariable logistic regression analysis. Multivariable logistic regression analysis demonstrated that lower apelin levels and diminished eGFR were associated with a higher VCS. Contrarily, higher levels of inorganic phosphorus and FGF-23 were linked with a higher VCSA.

Conclusions: The results suggest that apelin and FGF-23 are predictors of VC on type 2 diabetic patients with CKD. Therefore, these osteo-mineral markers might be used as diagnostic/therapeutic targets in order to improve management of CKD complications.

PO2465

Endothelial Dysfunction in Dermal Biopsies of Patients with CKD: Associates with Markers of Inflammation and Volume Overload

Background: Cardiovascular (CV) morbidity is a major health problem in patients with chronic kidney disease (CKD). Besides traditional risk factors, CKD-induced endothelial dysfunction (ED) is involved in CV pathology. Of note, the luminal side of the vascular endothelium is covered by a protective endothelial glycocalyx (eGC) and indirect evidence indicates eGC loss and/or ED in CKD patients. So far, no direct endothelial profiling in non-renal tissue from renal patients has been performed. We aimed to investigate possible eGC loss and ED in CKD patients and its association with inflammation and volume overload.

Methods: During kidney transplantation, abdominal skin biopsies were taken from 11 kidney transplant recipients, of which 4 received hemodialysis. Abdominal skin biopsies from 9 healthy kidney donors served as control. Biopsies were stained for the endothelial marker CD31. We also studied associations between the quantified endothelial markers and plasma markers of inflammation (CRP) and volume overload (NT-proBNP).

Results: Compared to healthy subjects, there was severe loss of eGC marker Ulex Europ and the endothelial markers VEGFR2 and vWF. Subsequently, they were quantified and normalized in an immunofluorescence double staining for the pan-endothelial marker CD31. We also studied associations between the quantified endothelial markers and plasma markers of inflammation (CRP) and volume overload (NT-proBNP).

Conclusions: This study is the first to show direct evidence of dermal ED in patients with CKD. eGC damage has been shown by loss of Ulex Europ 1 and endothelial activation by increased VEGFR2 and vWF levels. In line with previous research, our results show ED to associate with inflammation and volume overload. More research is needed to further explore this pathophysiology.

PO2466

CCN2/CTGF Causes Renal Fibrosis Progression Through the Integrin/FAK Signal Pathway
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Background: Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that accumulates with integrins at focal adhesions and is involved in intracellular signal transduction. We have focused on CCN2, and demonstrated that FAK phosphorylation is also reduced when the progression of fibrosis is suppressed in a tubular cell-specific CCN2 knockout mouse. In this study, we examined in greater detail the relationship between CCN2 and FAK.

Methods: A mouse ischemia-reperfusion (IRI) model, cultured human renal tubular epithelial cells (HK-2), 3 types of anti-phosphorylated FAK antibody (Y397, Y576/577, Y925), and anti-total FAK antibody were used to perform Western blotting. Furthermore, we examined what subunits of the integrin were expressed in HK-2 by using RT-PCR. A specific neutralizing antibody against integrin was also used to suppress the binding of U0126 to integrins.

Results: A significant increase in total FAK was observed in the chronic phase (day 12) as fibrosis progressed (total FAK/GAPDH; control 0.81 ± 0.10 vs. day 12 1.96 ± 0.20). Among the phosphorylated FAK (pFAK), Y397 was particularly significant (pFAK/FAK control 0.39 ± 0.01 vs. day 12 0.73 ± 0.17). Positive staining for pFAK was observed in tubular epithelial cells. In serum-stimulated HK-2, FAK was phosphorylated, but the addition of the decoy peptide of the CCN2 VI module decreased the amount of Y397. Results of RT-PCR confirmed the expression of several integrin subunits. The results of studies using neutralizing antibodies revealed that the decrease in pFAK was most marked when the anti-integrin αv antibody was added (pFAK/FAK control 0.99 ± 0.13 vs. 0.48 ± 0.06 after addition of the antibody).

Conclusions: By using the IRI model, we found that not only the expression of FAK was increased but also its phosphorylation was promoted in the injured kidney. CCN2 produced in tubular epithelial cells acts via cellular integrin αv in autocrine/paracrine manner, and promotes renal fibrosis through phosphorylation of the tyrosine 397 residue of FAK. CCN2 has been previously shown to activate Wnt/β-catenin and TGF/β/Smad pathways. However, here we identified another pathway for CCN2 in relation to kidney fibrosis. Several FAK inhibitors have already been investigated as anticaancer agents. Further clarification of the pathways may prove the therapeutic effects of these inhibitors on CKD.

Funding: Government Support - Non-U.S.

PO2467

Multitarget Soluble Epoxide Hydrolase/Farnesoid X Receptor Agonist Combats CKD
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Background: Chronic kidney disease (CKD) is characterized by progressive fibrosis leading to end-stage renal disease. There has been little success in developing agents that can slow the progression of CKD to ESRD. The current study investigated the efficacy of an innovative multi-target ligand drug, DM509, in mitigating renal fibrosis using the unilateral ureteral obstruction (UUO) mouse model.

Methods: DM509 acts concurrently as a soluble epoxide hydrolase inhibitor and farnesoid X receptor agonist. UUO or sham surgery was conducted in C57BL/6 male mice (n=8/group). Interventional DM509 treatment (10 mg/kg/day) or vehicle was started three days after UUO induction and continued for 7 days. Plasma and kidney tissue were collected at the end of the experimental protocol. Several biochemical, histopathological, immunohistochemical, and gene expression studies were carried out to determine the antifibrotic effects of DM509.

Results: UUO mice demonstrated fibrosis with higher kidney hydroxyproline content (267±60 vs. 53±14 μg/mg protein), collagen area (4.3±0.1% vs. 7.0±0.3%), and serum creatinine levels (3.0±0.1 vs. 2.5±0.0 mg/dL). Substantial reduction of hydroxyproline by 41% and collagen area by 53% was achieved with DM509 treatment. DM509 treated UUO mice further evidence in UUO mice with elevation of MCP-1, increased CD45 immune cells, and increased TNF-α, IL-6, IL-1β expression. Interventional DM509 treatment markedly reduced renal inflammation in UUO mice. Vascular inflammation was evident in UUO mice with increased higher ICAM and VCAM expression. DM509 reduced vascular inflammation by 40-50% in UUO mice. In addition, peritubular vascular density assessed by CD31 was reduced by 35% in UUO mice and DM509 attenuated vascular loss. Kidney fibrosis in UUO mice was associated with epithelial-to-mesenchymal transition (EMT) with higher expression of mesenchymal markers a-SMA, FSP-1, and FN, as well as a marked decrease in the epithelial marker, E-cadherin. UUO mice treated with DM509 had markedly reduced EMT. UUO mice also had tubular epithelial barrier injury with increased renal KIM-1, NGAL expression and lower claudin-1, -2 and -4 expression. DM509 treatment reduced tubular injury markers by 25-50% and maintained tubular epithelial integrity by restoring claudin expression in UUO mice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: These data reveal that DM509 is a promising multi-target anti-fibrotic drug that can reduce epithelial and vascular kidney fibrotic disease and CKD progression.

Funding: NIDDK Support

PO2468
Single-Nucleus Transcriptional Profiling of CKD After Repeated Low-Dose Cisplatin Treatment
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Background: Cisplatin induces both acute and chronic kidney problems during chemotherapy. Recent studies have established the models of chronic kidney problems after repeated low dose cisplatin treatment (RLDC). RLDC-induced global transcriptional changes in specific renal cells associated with the development of chronic kidney problems is unclear.

Methods: Male C57BL/6 mice were given 4 consecutive weekly injections of 8 mg/kg cisplatin. Renal function was measured at 5 and 9 weeks after the first cisplatin injection. Kidney tissues were collected for histology and single-nucleus RNA sequencing (SnRNA-seq). Cell-type-specific changes in gene expression were compared between the samples from control and cisplatin treated mice. Transcriptional regulators in proximal tubular cells were identified and qPCR was used to validate the critical genes involved in renal fibrotic and inflammation.

Results: RLDC induced decreases in eGFR and kidney weight in mice at 5 and 9 weeks. The kidneys of these mice showed tubular degeneration and dilation. There was also increases in KIM-1 positive tubules and atubular glomeruli. Sn-RNA-seq identified transcripts corresponding to 23021 genes. The markers for 11 cell types and 12 cell clusters were detected. Cluster-by-cluster comparison demonstrated cell-type-specific changes in gene expression that are important for transport, fibrosis and inflammation in RLDC mouse kidneys. In particular, compared with the untreated control, RLDC resulted in 425 differentially expressed genes (log2FC=1, p<0.05) in proximal tubular cells. The top 9 marker genes displaying altered expression were enriched in profibrotic and proinflammatory pathways, respectively. Consistently, RLDC induced NF-κB activation and proinflammatory cytokines (TNFα, IL6 and IL17), and the expression of fibrosis markers (fibronectin, collagen I, vimentin and α-SMA). Furthermore, Runx1 and Snail were identified as transcriptional factors that drive inflammation and fibrosis progression after repeated cisplatin treatment.


Funding: NIDDK Support, Veterans Affairs Support

PO2469
Activation of EGFR in Myofibroblasts Promotes Renal Fibrosis in Unilateral Ureteral Obstruction
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Background: In response to injury, renal fibroblasts and pericytes differentiate into highly specialized myofibroblasts, which are essential for maintaining kidney structural integrity. It is imperative to understand the molecular mechanism initiating and sustaining myofibroblast activation in order to identify novel therapeutics to stop or reverse kidney fibrosis. The activation of epithelial growth factor receptor (EGFR) plays an important role in mediation of recovery of epithelial integrity following ischemic acute kidney injury (AKI). However, sustained activation of EGFR triggers renal fibrogenesis after AKI. The role of EGFR in fibroblast/myofibroblast development in renal fibrosis after severe AKI has not been previously investigated.

Methods: Both PDGFRαCreERT2; mCherry mice (WT) and PDGFRαCreERT2; mCherry; EGFR-/- mice (PDGFRαCreERT2; mCherry; EGFR-/-) were treated with tamoxifen 2 weeks before unilateral ureteral obstruction (UUO) to create PDGFRαCreERT2; mCherry; EGFR-/- mice, selective EGFR deletion was confirmed by >80% EGFR mRNA reduction in isolated renal PDGFRα+ cells. EGFR mRNA and protein were measured by qPCR and Western blot in both wild-type and PDGFRαCreERT2; mCherry; EGFR-/- mice at day 3 after UUO. PDGFRα+ positive cells were isolated using PDGFRα antibody/ IgG microbeads.

Results: EGFR mRNA in isolated renal PDGFRα+ cells was increased <5-fold after 7d UUO. In PDGFRαCreERT2; mCherry; EGFR-/- mice, selective EGFR deletion was confirmed by >80% EGFR mRNA reduction in isolated renal PDGFRα+ cells as well as absence of immunofluorescent EGFR expression in α-SMA+ myofibroblasts. Flow cytometry determined that renal C4D7CD31PDGFRα+αSMA+ cells were markedly lower in PDGFRαCreERT2; mCherry; EGFR-/- mice than WT mice 3d after UUO. PDGFRαCreERT2; mCherry; EGFR-/- mice had markedly decreased renal fibrosis, indicated by Sirius red and Masson’s trichrome staining, and increased mRNA and protein levels of profibrotic and fibrogenic components including α-SMA, collagen I, collagen IV, IL-11, fibronectin, and PDGFRRβ. Isolated PDGFRαCreERT2; mCherry; EGFR-/- cells also expressed less collagen I and collagen IV. Unexpectedly, the mRNA levels of proinflammatory cytokines, including Tnfα, Il6, Il1α,Il1b, Ccl2, Ccl3, Il23a, Ifng, and Il12 in whole kidney tissue as well as in isolated renal myofibroid cells were comparable between WT mice and PDGFRαCreERT2; mCherry; EGFR-/- mice.

Conclusions: In unilateral UUO, increased PDGFRα expression in PDGFRααCreERT2; mCherry; EGFR-/- mice induces myofibroblast proliferation and differentiation to promote subsequent fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

PO2470
Activins Facilitate TGF-β1 Profibrotic Signaling in Kidneys
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Background: Chronic kidney disease (CKD) is a rising health issue in North America and is characterized by irreversible renal fibrosis leading to end-stage kidney disease requiring dialysis or transplantation. TGFβ1 is a central mediator of kidney fibrosis in CKD of diverse etiology. Directly blocking it is impossible due to adverse effects. Alternate approaches to inhibit TGFβ1 signaling are needed to develop tolerable anti-fibrotic therapies. Recent studies suggest that TGFβ1 requires activins for its profibrotic effects. Interestingly, both signal through the same canonical Smad pathway. Here we study the mechanisms by which activins enable TGFβ1-induced fibrosis and assess efficacy of specific activin inhibition in vivo.

Methods: Primary mouse kidney mesangial cells (MCs) were used. Activin A and B (AA, AB), the predominant activins, were used with an neutralizing antibody or follistatin. ELISA, IF and IB were used to assess cytokine levels, signaling pathways and profibrotic responses. Smad3 transcriptional activity was assessed by CAGA12 luciferase reporter and the alpha smooth muscle actin (α-SMA) promoter luciferase. Unilateral ureteral obstruction (UUO) was created in mice overexpressing (OE) TGFβ1 or wild-type controls, and effects of neutralizing anti-AA antibody on kidney fibrosis was assessed.

Results: TGFβ1 stimulated the production of AA more than AB, and AA neutralization inhibited the profibrotic effects of TGFβ1. TGFβ1 provoked strong early Smad3 activation in MCs (0-24h), while AA did so later (24-48h). Inhibition of AA decreased TGFβ1 (24h)-induced Smad3 activation, assessed by its phosphorylation, nuclear accumulation, and transcriptional activity. Cells retained responsiveness to AA signaling even after becoming refractory to TGFβ1 restimulation, enabling ongoing Smad3 activation. AA additionally regulated noncanonical TGFβ1 signaling. Its inhibition reduced nuclear accumulation of MRTFA, a Smad3 co-mediator of α-SMA induction by TGFβ1. Fibrosis was augmented in TGFβ1 OE mice. Neutralizing AA attenuated Smad3 activation and fibrosis in both wild-type and TGFβ1 OE mice.

Conclusions: AA facilitates TGFβ1 profibrotic effects through regulation of both canonical (Smad3) and non-canonical (MRTFA) signaling. Importantly, AA inhibition reduced fibrosis in vivo, suggesting a novel potential therapeutic for fibrosis in CKD.

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753
PO2472
ROCK-Binding ASD2-Domain of Shroom3 Has a Profibrotic Role
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Background: We previously showed that a CKD-associated Shroom3 allele was a quantitative trait locus for SHR2OM3 expression and promoted CKD and allograft nephropathy.

Methods: Here we investigated the mechanism of increased fibrosis downstream of Shroom3. We systematically deleted consensus domains in Shroom3 and evaluated profibrotic signaling in tubular cells (Fig 1).

Results: Overexpression of ASD2-domain deleted Shroom3 mutant (ASD2-SH3 with deficient ROCK binding) consistently reduced TGF-B signaling responses in TGB-B reporter 293-Tcells and in Smad-reporter luciferase assays (vs ASD1, PDZ-, Fyn-binding domain deletion mutants and intact SHR2OM3; n=3 sets each). Based on these data we generated doxycycline inducible transgenic mice for SHR2OM3 and ASD2-SH3 mutants. Two founder lines of each transgene crossed with CAGS-rtTA mice were selected based on transgene expression in kidney tissues upon DOX-feeding. Adult CAGS-rtTA/SHROOM3-Tg, ASD2-SH3-Tg and control mice were dosed and, and UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each).

Conclusions: Our sequential findings show that the profibrotic role of Shroom3 excess is mediated via its ASD2-domain.

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PO2473
EPAC1-Mediated cAMP Signaling in Podocytes Protects Kidneys from the Progression of Glomerulonephritis
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Background: Many efforts are made to identify new therapeutic targets to slow down, prevent or even reverse Chronic Kidney Disease (CKD) progression. One of the therapeutic approaches is the targeting of the represorptive cAMP pathway, especially by stimulation of its downstream effector, the protein kinase A (PKA). PKA was considered as the unique cAMP effector, however, the exchange factor directly activated by cAMP (EPAC1) is now recognized as a novel, PKA-independent, mediator of cAMP signaling. Epac1 is a guanine exchange factor that promotes the exchange of GDP for GTP regulating important cellular functions. Of the two isoforms described, Epac1 is the most expressed in the kidney. Epac1 activation exerts a renoprotective effect during acute kidney injury, via maintenance of epithelial adhesion and protection from oxidative stress. However, the role of EPAC1 in CKD remains poorly understood.

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PO2474
A Novel Allosteric HIPK2 Inhibitor Attenuates Renal Fibrosis with Superior Pharmacokinetic, Selectivity, and Safety Profiles
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Background: Renal fibrosis is considered the final convergent pathway for proteinuric kidney diseases, regardless of the original etiologies of the disease. Although much has been learned of the molecular mechanisms underlying renal fibrogenesis, there is still a paucity of success in translating this knowledge to clinical application. We previously demonstrated HIPK2 as a multifunctional activator of TGF-β/Smad3, NF-κB, and p53 pathways and that the global knockout of HIPK2 in mice attenuated kidney fibrosis in vivo. We recently developed a small molecule inhibitor of HIPK2, BT173, that specifically blocked TGF-β/Smad3 pathway to attenuate renal fibrosis without causing adverse systemic effects. Importantly, BT173 did not alter the activity of p53 to produce unwanted oncogenic side effects. However, the in vivo use of BT173 was limited by its poor solubility and potency.

Methods: Based on BT173, we used iterative cycles of chemical synthesis and biological assays to optimize the solubility, bioavailability and potency of TGF-β/Smad3 pathway inhibitor. ADME, selectivity, and safety profiling were performed on the optimized HIPK2 inhibitor compounds. The lead inhibitor was then tested in CKD models to test its efficacy in reducing renal fibrosis.

Results: 1) Repeated iteration and in vitro screening assay led to a lead compound, HIPK2-174. 2) HIPK2-174 showed greater potency (IC50=200nM) to disrupt the HIPK2-Smad3 interaction in vitro with enhanced solubility. 3) It showed pharmacokinetics suitable for oral qd dosing. 4) No appreciable kidney inhibition was observed when tested against a panel of 30 diverse kinases. Acceptable selectivity profiles were observed with Eurofins Safety 44 and CEREP selectivity panels. 5) Safety profiling did not show any relevant CYP inhibition, hERG, or other cardiac ion channel liabilities. 6) Daily qd dosing of HIPK2-174 in mouse models of proteinuric CKD significantly reduced proteinuria and renal fibrosis development.

Conclusions: The optimized HIPK2-174 effectively improved renal function, reduced renal fibrosis development and CKD progression in vivo. Moreover, its enhanced selectivity, bioavailability, and biological activity demonstrate a favorable safety profile in preclinical species for IND-enabling studies.

Funding: Commercial Support - ShangPharma Innovation Inc.

PO2475
Inhibition of RNA-Binding Protein HuR Protects Kidney from Ischemia-Reperfusion-Induced Injury and Fibrosis
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Background: Upregulation of an RNA-binding protein HuR has been implicated in glomerular diseases both in patients and in animal models. Herein, we further evaluated whether upregulation of HuR contributes to renal injury and subsequent fibrosis by using a renal ischemia/reperfusion (IR) mouse model and a selective HuR inhibitor, KH3.

Methods: All mice were received unilateral renal IR surgery for 35 minutes. The contralateral kidneys without surgery served as controls. Mice were then randomly assigned into either vehicle or KH3-treated groups (n=5/group). KH3 was given via daily intraperitoneal injection from day 3 after IR at the dose of 50 mg/kg/day to day 14. In addition to the effect of IR injury on TGFβ-induced tubular cell injury was further investigated in vitro.

Results: IR-injured kidneys showed a significant upregulation of HuR in tubular and tubulointerstitial cells determined by positive cytoplasmic staining of HuR and western blot assay, which was accomplished by extensive tubular damage and fibrosis. However, KH3-treated and IR-injured kidneys exhibited greatly reduced damage and fibrosis, and this correlated with a reduction in renal expression of profibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition (EMT), and apoptosis. A panel of 760 fibrosis-associated genes were further assessed, revealing that 519 genes in mouse kidney following IR injury changed their expression and 71.3% of those genes that are involved in 50 annotated...
pathways were ameliorated when treated with H13. Among those, TGFβ1 as a Hu target was elevated in the IR-injured kidney. K13-harbored TGFβ1-induced tubular Hu cytokinotropic translocation and subsequent tubular EMT in cultured HK-2 cells.

**Conclusions:** These results suggest that upregulation of HuR contributes to renal tubular injury and fibrosis by dysregulating multiple pro-fibrotic pathways. HuR-targeted inhibitory therapeutics offer promising novel treatment in the future for preventing or reversing the progression of CKD.

**Funding:** NIDDK Support

**PO2476**

**Spiny Mice (Acomys cahirinus) Activate Unique Transcriptional Programs After Severe Kidney Injuries and Regenerate Organ Function Without Fibrosis**

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**Background:** Fibrosis-driven solid organ failure is a pervasive burden on global health. Rodents of the genus Acomys (spiny mice) are terrestrial mammals that evolved remarkable abilities to regenerate severe skin wounds without scar formation to avoid predation. Whether regenerative wound healing extends beyond skin to vital internal organs in spiny mice is not known.

**Methods:** Models of acute and chronic kidney injury (UO, unilateral IRI, unilateral IR, nephrectomy) were utilized in Acomys and compared to C57Bl6/J and CD-1 mice. Fibrosis, myofibroblasts, macrophages were measured. Total kidney RNA Seq, western blotting and confocal image analysis was performed.

**Results:** Using two aggressive kidney injury models, we show that despite equivalent kidney injury, there is a significant regeneration of nephron structure and function without fibrosis in Acomys compared to extensive fibrosis and renal failure in Mus. Comparative genome-wide analysis of gene expression after injury suggested that the Acomys genome is poised to initiate and sustain regenerative wound healing. Among the 843 differentially regulated genes between Acomys and Mus were metabolic enzymes, transcription factors, and nongenomic genes such as Oxtr, 1R, 2R, and Cdkb. Analysis revealed 6 clusters of genes that were differentially regulated with injury between Mus and Acomys. Clusters 1 and 4 represented Mus-specific genomic responses to UO injury whereas the responses in injury in Acomys is to maintain expression at homeostatic levels. In contrast, clusters 2 and 3 represent Acomys-specific kidney response gene sets which are unchanged or downregulated in Mus. Early after injury, a cluster 3 gene, Cdh6 appeared in rapidly expanding renal tubular mosaic patches throughout the injured Acomys, but not Mus. Repression of nephron function was observed as decreased cell cycle entry and DNA replication in tubular and glomerular cells, including podocytes and endothelial cells.

**Conclusions:** Our findings have important implications for an evolutionary solution to mammalian regenerative repair of the kidney, and by extension, to the heart and coronary vessels, lungs, liver and other internal organs similarly prone to organ failure as a result of progressive tissue fibrosis.

**Funding:** NIDDK Support, Other NIH Support - DiaComp

**PO2477**

**Graphene Quantum Dots Protects Against Renal Fibrosis After Restoring Mitochondria Function in Rat 5/6 Nephrectomy**

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**Background:** Graphene Quantum Dots (GQDs) are carbon-based nanoparticles and spotlighted in biological application due to their biocompatibility, quantum confinement, and low toxicity. Rat with subtotal 5/6 nephrectomy exhibit mitochondrial dysfunction mediated by TRPC5 channel, a core calcium channel in podocytes and tubular cells. With current limited understanding of the interaction between nonnatorials and renal cells, we show GQDs as a potential therapeutic nano-sized material in 5/6 nephrectomy rat model.

**Methods:** To evaluate GQDs therapeutic effect 5/6 nephrectomy Sprague Dawley (8-week; male) rat model, GQDs (4mg/kg) was administered by intraperitoneal for 5 times per week up to 3 weeks. In vivo stimulation experiment, representative TRPC5-beta (2mg/mL) was treated in both human primary podocytes and tubular cells with GQDs in dose-dependent manner (0.1ug/mL, 0.5ug/mL, 1ug/mL). Renoprotection in 5/6 nephrectomy were assessed through combination of flow cytometry, Annexin V – FTIC apoptosis staining, histomorphometry, functional manipulations, protein and mRNA expressions.

Intracellular Calcium permeability was measured from Fura 2-AM.

**Results:** GQDs pivotal role in 5/6 nephrectomy led to identification of the partial proteumuria recovery and antihypertensive effects. In Vivo study discloses GQDs anti-fibrotic as improved kidney function process that co-express macrophage (CD68) and myofibroblast (a-SMA). Thus, in vitro study after TRPC5-beta induction show similar results. GQDs-treated group in rats have increased potential cell viability by downregulating the catalytic kinase inhibitors after decreasing Bax-2, P53, P21 but increasing BCL2 expression.

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**Funding:** NIDDK Support, Veterans Affairs Support - DiaComp

**PO2478**

**Critical Role of Histone Demethylase JMJD3 in the Regulation of Macrophage Polarization and Renal Fibrosis**

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**Background:** Chronic kidney disease is characterized by macrophage infiltration and fibrosis. Macrophage infiltration and polarization play an important role in the development of renal fibrosis. However, the mechanisms underlying macrophage polarization and development of renal fibrosis are not fully understood. In this study, we examined the role of histone demethylase JMJD3 in the regulation of macrophage polarization and renal fibrosis.

**Methods:** To examine the role of JMJD3 in vivo, we generated mice with global or myeloid cell-specific deletion of JMJD3, and we treated wild-type mice with vehicle or GSK-J, a selective JMJD3 inhibitor. Unilateral ureteral obstruction (UUO) model were used to induce renal fibrosis.

**Results:** JMJD3 expression was increased in the kidneys during the development of renal fibrosis. Mice with tamoxifen-inducible deletion of JMJD3 (CAG-Cre, floxed JMJD3) or myeloid cell-specific deletion of JMJD3 (Ly5-Cre, floxed JMJD3) were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed JMJD3 mice, mice with global or myeloid cell-specific deletion of JMJD3 displayed fewer F4/80-positive macrophages, CD206-positive M2 macrophages, and myofibroblasts, and expressed less α-SMA protein in the kidneys following UUO. Furthermore, global or myeloid cell-specific deletion of JMJD3 significantly reduced total collagen deposition and ECM protein production in the kidneys after UUO injury. Real-time RT-PCR showed that global or myeloid cell-specific deletion of JMJD3 attenuated M2 macrophage polarization, fibroblast activation, and extracellular matrix protein production. Moreover, genetic deletion of JMJD3 increased histone Lys 27 dimethylation. Wild-type mice treated with GSK-J4 exhibited fewer M2 macrophages and myofibroblasts and produced less amounts of extracellular matrix proteins in the kidney following UUO.

**Conclusions:** Our study identifies JMJD3 as a critical regulator of macrophage polarization and development of renal fibrosis. Therefore, JMJD3 may represent a novel therapeutic target for chronic kidney disease.

**Funding:** NIDDK Support, Veterans Affairs Support

**PO2479**

**DNA Methylation in Repeated Low-Dose Repeated Cisplatin-Induced CKD**

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**Background:** DNA methylation is an epigenetic mechanism that regulates gene expression by adding methyl groups to DNA molecules via DNA methyltransferases (DNMT) and DNA methylation changes have been implicated in the pathogenesis of kidney diseases. Recent work indicates that DNA methylation protects against cisplatin-induced acute kidney injury partially through hypomethylation of interferon regulatory factor 8 (Irif8). However, little is known about DNA methylation in chronic kidney disease problems following cisplatin exposure.

**Methods:** Mice and HK2 cells were subjected to repeated low-dose cisplatin treatment (RLDC). We analyzed the expression of DNMTs and the methylation marker 5-methyl-cytosine following RLDC. We further conducted representation bisulfitie sequencing (RRBS) to analyze the genome-wide DNA methylation changes. To explore the pathogenic role of DNA methylation, we initially tested the effects of 5-aza, a pharmacological DNMT inhibitor. We further established and tested a conditional knockout mouse model in which DNMT3a is specifically ablated from kidney proximal tubule (CD1 mice; DNMT3a-KO).

**Results:** RLDC induced notable increases in DNMT1 and DNMT3a (but not DNMT3b) expression, which were accompanied by an overall increase in DNA methylation as shown by 5-methyl-cytosine staining. Genome-wide DNA methylation changes were analyzed differently methylated regions (DMRs) in 171 genes after RLDC. Five of these genes (Oxgr1, Smuin22, Sech2a1, Ihl, Nudl) had hypermethylation in their promoter regions, which was associated with decreased mRNA expression, suggesting the regulation of these genes by DNA methylation. Functionally, 5-aza reduced the expression of these DNA methylation-related proteins in Acute stimulation of these regions including collagen I and CTG.

In vivo, 5-aza and ablation of proximal tubule DNMT3a both alleviated the decline of renal function, kidney atrophy, and renal fibrosis after repeated cisplatin treatment.

**Conclusions:** DNMTs are induced in renal tubular cells after cisplatin exposure, accompanied by an overall increase in DNA methylation. Under this condition, DNA methylation contributes to the development of chronic kidney problems. Inhibition of DNMTs may afford therapeutic effects against cisplatin-induced chronic kidney disease.

**Funding:** NIDDK Support, Veterans Affairs Support, Private Foundation Support, Clinical Revenue Support
PO2480
Targeting Histone Demethylase LSD1 Inhibits Renal Epithelial-Mesenchymal Transition and Attenuates Renal Fibrosis
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Background: Lysine-specific histone demethylase 1 (LSD1) as the first identified protein demethylase plays a special role in the regulation of gene expression by removing methyl groups from mono- and di-methylated lysine 4 and 9 on histone H3 and functions as an oncogenic factor in cancers. However, its role in renal fibrosis is unknown.

Methods: To evaluate the role and mechanisms of LSD1 in the development of renal epithelial–mesenchymal transition (EMT) and renal fibrosis, we inhibited LSD1 with its inhibitor, ORY1001, in mouse unilateral ureter obstruction (UUO) model and rat kidney fibroblasts (NRK-49F) and rat kidney proximal tubular (NRK-52E) cells stimulated by TGF-β1.

Results: We found that the expression of LSD1 was increased and the methylation of its histone targets were decreased in mouse kidneys with unilateral ureteral obstruction and NRK-52E cells undergoing EMT. Inhibition of LSD1 with ORY1001 decreased the deposition of extracellular matrix proteins and the expression of fibrotic markers, including α-smooth muscle actin (α-SMA) and fibronectin, which was associated with preserving E-cadherin expression and inhibiting N-cadherin upregulation in the obstructed kidney. Injury to the kidney enhanced the phosphorylation and activation of Smad2/3, AKT and Stat3, and that could be prevented by ORY1001 administration. Targeting LSD1 with ORY1001 and siRNAs inhibited TGFβ1-induced the activation of renal fibroblasts, NRK-49F, and EMT of NRK-52E cells. The expression of Snail family transcriptional repressor 1 (Snail-1) was upregulated in UUO kidneys and cultured NRK-52E cells treated with TGFβ1. Snail-1 repressed the expression of E-cadherin via the interaction of its N-terminal SNAG domain with LSD1. LSD1 inhibition with ORY1001 or siRNA silencing prevented the upregulation of Snai1 and disrupted Snail/LSD1 interaction, resulting in the expression of E-cadherin. ORY1001 was also effective in suppressing TGFβ1-induced renal epithelial cells arrest at the G2/M phase.

Conclusions: This study indicates that LSD1 participates in the expression of profibrotic genes and contributes to renal EMT and fibrosis through activation of diverse signaling pathways, and places an emphasis that LSD1 has potential as a therapeutic target for the treatment of renal fibrosis.

Funding: Other NIH Support - R01 DK084097, R01 DK126662 and NIH P30 DK106912

PO2481
Does Senescence Induce Muscle Wasting in CKD?
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Background: Muscle wasting is a common complication of CKD and associated with higher mortality and morbidity. The mechanism of muscle wasting in uremia has been widely studied; however, uremic stress-induced senescence might be a missing connection between chronic kidney disease and muscle wasting. Senescent cells are capable of producing and secreting various growth and proinflammatory factors, cytokines, and chemokines, which is known as the S-ASP. We hypothesized that senescence and senescence associated secretory phenotype (S-ASP) play important roles in the CKD-induced muscle loss.

Methods: CKD mice were induced by 5/6 nephrectomy. Senescence was confirmed by using senescence associated beta gal (SA-βgal); and 4) S-ASP components present in the uremic muscle, which include high levels of interleukin 6 (IL-6), TNFα, TGFβ and IL-8. The CKD-induced elevation of cytokines were measured by ELISA. Senescence pathway markers p16, p21 and p53 were measured by Western blots. To limit senescence, dasatinib (5 mg/kg) or quercetin (50 mg/kg BW) (D&Q) were given by oral gavage 2 days per week for 8 weeks. Muscle function was measured with a grip force detector.

Results: CKD stress-induced premature senescence phenomena have been evidenced in the skeletal muscle of uremic mice by the increases in senescence pathway indicators (p21 and p16, but not p33 protein; 2) phosphorylated histone H2AX (γH2AX, DNA damage marker); 3) the level of the senescence biomarker SA-β-gal, and 4) S-ASP components present in the uremic muscle, which include high levels of interleukin 6 (IL-6), TNFα, TGFβ and IL-8. The D&Q treatment reduced IL-6 and TNFα levels. The D&Q treatment compared with the vehicle treatment in 5/6 nephrectomy mice. Skeletal muscle function was also improved with D&Q treatment in uremic mice.

Conclusions: Senescent and S-ASP are important factors in development of muscle wasting during CKD progression. Limiting senescence with D&Q ameliorates muscle wasting and improves muscle function. These results provide new approaches for developing therapeutic strategies to improve muscle health in chronic kidney diseases.

Funding: Veterans Affairs Support

PO2482
Chronic Aristolochic Acid Administrations Induce Renal Senescence in Mice
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Background: The kidneys are one of the most susceptible organs to age-associated impairments. Recently, although renal aging research has been extensively performed, appropriate models of renal aging are still limited. Generally, renal aging is strongly associated with renal fibrosis, which is the final common pathway of chronic kidney disease. Aristolochic acid (AA), a renal toxic agent, causes aristolochic acid nephropathy (AAN) characterized by progressive renal fibrosis and functional decline. Here, we examined the potential of AAN as a model of renal senescence using chronic AA administrations into C57BL/6 mice.

Methods: 8-week-old male C57BL/6 mice were assigned to AA or vehicle control groups after 1-week acclimatization. Mice were intraperitoneally administered with AA (3mg/kg) or vehicle (75% dimethyl sulfoxide) twice a week for 4 weeks, followed by a 4-week recovery period.

Results: Compared to controls, the AA group showed aged kidney-like phenotypes such as reduced atrophy, renal functional decline, and tubulointerstitial fibrosis. In addition, AA provoked cellular senescence specifically in the kidneys, concomitant with an increase in renal p16 mRNA expression and senescence-associated β-galactosidase activity. Additionally, AA-induced mice exhibited proximal tubular mitochondrial abnormalities, followed by accumulation of reactive oxygen species.

Conclusions: Collectively, the results of the present study indicates that AA partially mimics aged kidney and could become a useful mouse model for kidney aging research.

Figure 4

PO2483
Hypervitaminosis A Contributes to Kidney Injury Through Excessive Endoplasmic Reticulum Stress in CKD
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Background: Endoplasmic reticulum (ER) stress is activated upon the accumulation of misfolded proteins in the ER. PERK signal, one of the downstream pathways of ER stress response, mediates some transcription factors such as activating transcription
factor 4 (ATF4) and C/EBP-homologous protein (CHOP). It has been known CHOP induction in renal fibrosis and leads to chronic kidney disease (CKD) via apoptosis. ATP4 promotes transcriptional activation of DNA damage-inducible protein 34 (GADD34/Ppp1r15a), which is the negative-feedback protein of PERK signaling and essential for cell survival. It is reported that the levels of plasma vitamin A and its metabolites, all-trans retinoic acid (ATRA) and 13-cis retinoic acid (13-cis RA) were increased in the CKD stage. One recent report shows excessive vitamin A in CKD patients induces renal dysfunction, however, the effects of ATRA on ER stress have been unclear. In this study, we investigated the role of ATRA on ER stress in the kidney.

Results: Although ATRA did not change the mRNA and protein expressions of ATF4 and CHOP in NIH3T3 cells, ATRA additively increased ATF4 and CHOP induced by Tg. Interestingly, ATRA decreased GADD34 protein expression induced by Tg, even though ATRA increased Tg-induced expression of ATF4, the positive upstream regulator of GADD34. The evaluation of Masson's Trichrome staining in the kidney suggested ATRA increase CKD-induced fibrosis.

Conclusions: This report shows excessive vitamin A in CKD patients induces renal dysfunction, however, the effects of ATRA on ER stress have been unclear. In this study, we investigated the role of ATRA on ER stress in the kidney.

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Conclusions: D-Serine is a physiological molecule that promotes kidney remodeling. Besides its functions as a biomarker, D-serine has a physiological activity that influences kidney function.

Funding: Commercial Support - Shiseido Company, Limited, Government Support - Non-U.S.

PO2489
First-in-Class PRS Inhibitor DWN12088 Ameliorates Folic Acid-Induced Kidney Fibrosis

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Background: Fibrosis is characterized by the upregulated extracellular matrix (ECM), which drives organ damage and abnormal cell proliferation. According to recent studies, PRS (prolyl-riNA synthetase) is known to play a role in synthesizing collagen during ECM components. It has been reported that PRS is greatly increased in the lung and liver fibrosis animal model, but the role of PRS in the renal fibrosis model has not been elucidated.

Methods: In this study, we investigated the protective effect of novel PRS inhibitor (Daewoong Pharmaceutical Co., Ltd, Korea), in folic acid (FA)-induced kidney fibrosis and aimed to determine whether this role depends on the inhibition of mitochondria dysfunction and the STAT3 signaling pathway. Renal fibrosis was induced by FA (250 mg/kg) intraperitoneal injection in C57BL/6 mice. DWN12088 (10, 30 mg/kg) was administered by intraperitoneal daily injection for 4 weeks. Histological changes were examined by Masson’s trichrome staining. The expression of ECM markers was evaluated by immunohistochemistry, western blot analysis and real-time PCR. Mitochondria was also examined by electron microscopy.

Results: FA induced renal fibrosis and mitochondria dysfunction and upregulated PRS expression. When the FA induced decreased weight in mice, there was an effect on body weight by administering the DWN12088. We also examined the blood urea nitrogen (BUN), serum creatinine (Cr), creatinine clearance (CCR) and urine protein creatinine ratio (UPCR) levels. DWN12088 attenuated the levels of clinical data of renal injury (it decreased BUN, Cr levels and UPCR levels, and increased the CCR levels). The administration of DWN12088 decreased the PRS levels and improved FA-induced renal fibrosis and mitochondria. Moreover, DWN12088 effectively inhibited the ECM markers (FN and Collagen 1A1) and the levels of SIRT1/STAT3 induced by TGF-β1 induced fibrogenesis in HK-2 cells. DWN12088 also improved mitochondria function in HK-2 cells.

Conclusions: This study provides evidence for the detrimental role of upregulated PRS in the pathogenesis of renal fibrosis. The findings highlight a DWN12088 that improves renal fibrosis and mitochondria dysfunction. As a result, blockade of PRS is a potential therapeutic intervention to prevent renal fibrosis (NRF-2020R1A2C2003438).

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PO2489
AIM2 Modulates Renal Metabolic Profile and Inflammation in Acute and Chronic Kidney Injury

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Background: The absent in melanoma 2 (AIM2) is cytosolic double-stranded DNA receptor expressed in the kidney. AIM2 activation initiates the assembly of the inflammasome, culminating in inflammatory response. Inflammomas cause metabolic dysregulation and drive pathology in a wide variety of human diseases. So far, the function and how AIM2 affects inflammatory and renal metabolic profile in acute and chronic injury is poorly described.

Methods: The wild-type (WT) and AIM2 KO mice were submitted to cisplatin-induced acute kidney injury or unilateral ureter obstruction (UUO), a chronic kidney disease model. We evaluated renal structure and function, fibrotic molecules, fibronectin (FN) and type 1 collagen (COL1) and inflammation (IL-1β, IL-6). The expression of carmine palmitoyltransferase 1 (CPT1α), involved in fatty acid oxidation (the main energy source of kidneys), and glycolytic enzyme expression, pyruvate kinase M2 (PKM2) were used as an indicative of metabolic alteration. The AIM2 activation was also investigated in proximal tubular cells (PTCs).

Results: The severe tissue injury induced in WT mice by cisplatin was markedly attenuated in AIM2 KO mice, evidenced by reduction in tubular dilatation and amelioration of renal function. Moreover, AIM2 deletion impaired the reduction of CPT1α expression. In the model of UUO, we observed an increase of AIM2 expression, concomitantly with increase of IL-1β, IL-6, FN and COL1. Moreover, the animals presented reduction of CPT1α and increase of PKM2, suggesting a metabolic reprogramming in the kidneys. The AIM2 deficiency attenuated the renal injury, fibrosis, inflammation, and CPT1α levels despite change after kidney injury. In vivo study, the AIM2 activation caused metabolic reprogramming in PTCs, accompanied by increase of proinflammatory and profibrotic markers.

Conclusions: AIM2 activation drives acute e chronic kidney injuries. However, a better understand on how AIM2 affects PTCs metabolism and its connection with inflammation and kidney injury is needed.

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PO2490
Identification of Post-Translational Guanidinylated Proteins in the Context of Systemic Lupus Erythematosus by Using Mass-Spectrometric Methods

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Background: With continuous identification of post-translational modified isoforms of proteins, it is becoming increasingly clear that post-translational modifications limit or modify the biological functions of native proteins are majorly involved in development of various chronic disease. This is mostly due to technically advanced molecular identification and quantification methods, mainly based on mass spectrometry. Mass spectrometry has become one of the most powerful tools for the identification of proteins and peptides.

Methods: In this study, we used sophisticated high-resolution mass-spectrometric methods to analyze the soluble ligand of receptor Notch-3, namely the Y-box protein (YB)-1, in serum from systemic lupus erythematosus (SLE) patients. In addition, kidneys of lupus-prone (MRL.lpr/lpr) mice were analyzed by mass-spectrometric imaging techniques to identify the underlying pathomechanisms. Serum YB-1 was isolated by chromatographic methods, afterwards digested by trypsin and analyzed by matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS). The kidneys were fixed in paraffin, then kidney sections were deparaffinized, trypsin digested and analyzed by mass-spectrometric imaging techniques.

Results: Mass-spectrometry of extracellular YB-1 in SLE patient serum revealed post-translational guanidinylation of two lysine’s within the highly conserved cold shock domain (CSD) of the YB-1 protein (YB-1-2G). Patients with increased disease activity and those with active renal involvement (lupus nephritis, LN) had a higher degree of dual-guanidinyl synthesis within the CSD. Of note, at least one of these modifications was present in all analyzed LN patients, whereas single-guanidinylated YB-1 was present in only one and double modification in none of the control individuals. Mass-spectrometric imaging analyses specifically localized YB-1-2G and increases Notch-3 expression in kidney sections from MRL.lpr mice.

Conclusions: The data from this study clearly demonstrate the high potential of high-resolution mass spectrometric methods as well as mass spectrometric imaging techniques to identify pathomechanisms of diseases like SLE/LN.

PO2491
Deletion of Tubular Cpt1a Does Not Worsen Kidney Aging or Response to Injury

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Background: Proximal tubules (PT) preferentially use fatty acid oxidation to generate the energy necessary to support their high respiratory capacity. Carnitine palmitoyltransferase 1 (CPT1) is required for long chain fatty acids to enter mitochondria, and CPT1α is considered the rate-limiting enzyme for PT fatty acid oxidation. CPT1α expression is decreased in kidney injury and its overexpression reduces fibrosis, so we hypothesized that Cpt1a deletion would exacerbate kidney aging and injury.

Methods: We indelibly deleted Cpt1a in adult mouse tubules using Pax8-RTTA, tetO-Cre mice and confirmed robust recombination. Mice were aged for 2 years or injured by either aristolochic acid nephropathy (AAN) or unilateral ureteral obstruction (UUO). Primary PT-enriched cell populations were generated from aged mice, and fatty acid-dependent respiration and glycolysis were measured using Seahorse bioflux analyzer.

Results: Old mice lacking tubular Cpt1a (Cpt1a<sup>−/−</sup>) had increased intracellular fatty acid oxidation (Oil Red O staining) and inflammation (F4/80 staining), but there were no significant differences in oxidative stress, fibrosis or renal function (GFR, proteinuria) compared with aged controls. Similarly, Cpt1a<sup>−/−</sup> mice had no differences in tubular injury or fibrosis after either AAN or UUO-induced injury. Palmitate-dependent respiration was reduced but not blocked in primary cells from Cpt1a<sup>−/−</sup> aged mice, and glycolytic capacity was significantly increased. RNAseq from aged Cpt1a<sup>−/−</sup> revealed significantly upregulated genes in several pathways including PPARs that may compensate for Cpt1a loss.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2492
Multi-Omic Analysis of Mouse Renal Tubule Cell Responses Following Unilateral Nephrectomy
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Background: The kidney increases in size following resection of the contralateral kidney. Modern "omics" methods provide an opportunity to understand this response at a cellular level.

Methods: Experiments were done in mice after unilateral nephrectomy (UNx) or sham nephrectomy. MRI was used to measure kidney volume. The earliest portion of the kidney proximal tubule (PCT) and the cortical collecting duct (CCD) were microdissected at different time points (24 hours and 72 hours). Microdissected tubules were analyzed by quantitative immunofluorescence microscopy to determine cell size and number, and by RNA-seq to identify gene expression changes. Quantitative protein mass spectrometry was used to identify proteomic changes.

Results: Increased kidney volume was already detectable at the 24 hour-time point after UNx (versus sham), and was increased further at 72 hours. Morphometry of microdissected PCT and CCD, labeled with apical and basolateral markers and DAPI, revealed a marked increase in total cell volume per unit length, but no significant change in mean cell volume in both PCT and CCD, revealing that the increase in total cell volume was due to cellular proliferation rather than hypertrophy of individual cells. Consistent with this observation, RNA-Seq at 72 hours after surgery showed significant increases in the abundance of transcripts associated with cell cycle regulation in both segments (Gene Ontology enrichment analysis) such as Cdk1 and Cdc20 among many others. To identify the earliest signaling events, RNA-seq was employed at 24 hours after UNx revealing that in PCT, UNx produced upregulation of numerous transcripts associated with free fatty acid generation and sterol metabolism including many that are known targets of the transcription factor PPARα such as Angptl4, Acot1 and Cyp4a14. Protein mass spectrometry of whole kidneys at 24 hours, composed chiefly of proximal tubule cells, confirmed upregulation of many PPARα-regulated proteins such as HMGC2, CYP4A14 and ANGPT14.

Conclusions: Increased kidney size in response to UNx was due to cellular proliferation rather than hypertrophy of individual cells. Many lipid-metabolism related mRNAs were highly upregulated that predict increased free fatty acid levels in proximal tubule cells. Lipid mediators, including those derived from the fatty acid arachidonic acid, may be involved in the cellular proliferation.

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PO2493
Calponin 2 Determines AKI to CKD Transition Through Alternating Fatty Acid Oxidation
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Background: Calponin 2 (CNN2) is an actin filament-associated regulatory protein that plays a central role in numerous fundamental biological processes, including cell proliferation, motility, and adhesion to substrates and others cells. Emerging evidence suggests that cell mechanics can have direct, non-transcriptional influences on cell metabolism. The kidney is a highly metabolically active organ. Fatty acid oxidation is one of the major metabolic processes that occurred in the kidney under pathophysiological conditions. It remains unknown whether CNN2 plays a role in mediating kidney disease progression from the perspective of cell metabolism.

Methods: We constructed ischemic reperfusion injury (IRI) and unilateral ureteral obstruction (UUO) animal models in this study. In vivo and in vitro transcriptal experiments and proteomics were performed.

Results: Our quantitative proteomics revealed that CNN2 was induced at 1d and peaked at 10d after ischemic injury. In AKI or CKD patients' kidney biopsy specimens, CNN2 was upregulated and predominantly localized in the interstitial compartment. In vivo, knockdown CNN2 significantly preserved kidney function after ischemic AKI at 1 day. In two classic CKD models induced by 10-d IRI or 7-d UUO, the mice with CNN2 knockdown exhibited reduced expression of fibronectin, α-SMA, and collagen type I, compared to controls. In the meantime, Oil-Red staining showed reduced lipid accumulation in CNN2 knockdown mice kidneys than in controls. Mechanistically, we revealed that knockdown CNN2 could promote fatty acid oxidation to repair injured kidneys and subsequently halt disease progression, as assessed by the increased expression of FAO-related genes (PPARα, CPT1α, and ACOX1).

Conclusions: Our findings suggested that CNN2 is a crucial determinant in mediating the transition from AKI to CKD through alternating fatty acid oxidation.

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PO2494
Decreased Renal Gluconeogenesis Is a Hallmark of CKD
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Background: Chronic kidney disease (CKD) is associated with alterations of tubular function. Renal gluconeogenesis is responsible for 40% of systemic gluconeogenesis during fasting, but how and why this process is affected by CKD and the repercussions of such regulations are unknown.

Methods: We used data from more than 200 renal biopsies performed in CKD patients and from 43 kidney allograft patients. We studied three complementary mouse models of chronic kidney disease in vivo and ex vivo. We analyzed a cohort of patients having benefited from renal catherization and a retrospective cohort of patients hospitalized in the intensive care unit (ICU).

Results: Renal biopsies of CKD and kidney allograft patients revealed a stage-dependent decrease in the renal gluconeogenic pathway. Three different animal models of CKD confirm a proximal tubular cell-specific gluconeogenic down-regulation. This resulted in an alteration of renal glucose production and lactate clearance during an exogenous lactate load. Decreased renal glucose production and lactate clearance were confirmed by the isolated perfused kidney technique in animal models, and by renal venous catheterization in CKD patients. In CKD patients hospitalized in the ICU, systemic alterations of glucose and lactate levels were more prevalent and associated with increased mortality and worse renal prognosis at follow-up. Decreased expression of the gluconeogenesis pathway and its regulators predicted faster histological progression of renal disease in kidney allograft biopsies.

Conclusions: Renal glucose metabolism is impaired during CKD. Altered renal gluconeogenesis leads to systemic metabolic changes with a decrease in glucose and increase in lactate level, and associates with a worse renal prognosis.

Funding: Private Foundation Support, Government Support - Non-U.S.
Conclusions: MALDI MSI is potentially an effective tool for small molecule in situ analysis of human kidney tissue. MALDI-MSI technology, coupled with METASPACE, shed new light on omics data integration studies. In summary, from an individual patient with CKD, we found spatial restrictions of metabolites to normal tubule and potentially with atrophic tubule.

Funding: NIDDK Support

PO2498
Association of Metabolic Syndrome with Hyperfiltration in a General Non-Diabetic Population: The Renal Iloheol Clearance Survey

Background: Metabolic syndrome (MS) affects approximately one quarter of the world, making it a global epidemic. Although MS has been associated with increased risk of rapid decline in the glomerular filtration rate (GFR), only a few studies have investigated the association of MS with abnormally elevated GFR, known as hyperfiltration. Previous studies of MS and hyperfiltration were limited by the use of estimated GFR and the results were divergent. As there are promising treatment options for hyperfiltration, establishing the relationship between MS and hyperfiltration is of clinical importance.

Methods: In the Renal Iloheol Clearance Survey (REINS) we included 1551 subjects from the population based Tromso survey (2007-2009). The participants were 50-62 years old without known diabetes, cardiovascular disease or kidney disease. The GFR was measured using iohexol clearance. The aim was to investigate the relationship between MS and RHF. The dichotomous variable for RHF was defined as an absolute mGFR (ml/min) above the 90th percentile after adjusting for gender, age and height.

Results: Metabolic syndrome was associated with increased absolute GFR (ml/min) and renal hyperfiltration (yes/no) independent of age, sex and height (OR 2.44 95% CI 1.71 – 3.46, p<0.001). All risk factors except for hypertension were independently associated with RHF and increased absolute GFR. The risk of renal hyperfiltration was highest in subjects fulfilling 5 out of 5 criteria (OR 4.06, 95% CI, 1.54-10.67, p=0.005) compared to those fulfilling 0 or 1 criteria. Conversely, MS was not associated with higher estimated GFR based on creatinine or cystatin C.

Conclusions: Subjects with MS have a higher absolute GFR and increased risk of renal hyperfiltration compared to subjects without MS. RCTs are needed to explore whether treatment of hyperfiltration can prevent accelerated GFR decline and CKD in persons with MS.

PO2499
Hydrogen Sulfide Ameliorates High Fat Diet-Induced Hypertension and Kidney Injury in Mice
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Background: The role of hyperinsulinemia caused by high fat diet (HFD) in kidney injury is not known. Employing kidney proximal tubule specific insulin receptor (IR) KO mice, we have shown recently that HFD-induced kidney injury requires hyperinsulinemia-induced IR activation (Lee et al., JCI insight, 2021, 6(3): e143619). Furthermore, HFD reduced kidney hydrogen sulfide (H2S) generation in an IR-dependent manner. We tested if H2S administration ameliorates HFD-induced kidney injury in mice and cell models.

Methods: 5-month-old C57BL/6 male mice were placed on normal fat diet (NFD) or HFD for 2 months followed by randomization to receive for 2 months, H2S as sodium hydrosulfide (NaHS) 300 μmol/L in drinking water or water alone (n=5-6 in each group).

Results: HFD or NaHS did not affect blood glucose level. HFD increased body weight, and induced systolic hypertension (NFD: 118 ± 8 vs. HFD: 144 ± 10 mmHg), albuminuria (25.5 ± 16 vs. 139.7 ± 48 μg/mg), and kidney accumulation of matrix proteins. NaHS reversed these HFD-induced changes (systolic hypertension: 112 ± 7 mmHg; primary ACR: 76.1 ± 29 μg/mg) without affecting body weight. In the renal cortex, HFD reduced level of H2S, which was restored by NaHS administration. HFD stimulated IR phosphorylation and inhibited AMPK activity, which promotes synthesis of proteins including matrix proteins. NaHS did not affect IR phosphorylation but increased AMPK activity. We employed proximal tubule cells to test the effect of H2S on insulin-induced matrix synthesis. Insulin increased fibronectin synthesis likely through stimulation of its mRNA translation by inhibiting AMPK and activating mTORC1. This effect of insulin was abolished by NaHS.

Conclusions: Taking in vivo and in vitro data together, we conclude: (1) HFD induces kidney IR activation and reduces H2S generation in association with kidney injury. (2) H2S acts as a signaling molecule to activate AMPK, downstream of IR, and inhibits mTORC1 to ameliorate HFD-induced kidney injury. (3) H2S could be a therapeutic agent for obesity-related kidney injury.

PO2500
Proximal Tubule Cyclophilin D Mediates Kidney Fibrogenesis in Obstructive Nephropathy
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Background: Proximal tubule (PT) is highly vulnerable to acute injury, including ischemic insult and nephrotoxins, and chronic kidney injury. It is established that PT injury is a primary cause of development of chronic kidney disease, but the underlying molecular mechanism remains to be defined.

Methods: Here, we tested whether PT cyclophilin D (CypD), a mitochondrial matrix protein, is a critical factor to cause kidney fibrosis progression. To define the role of CypD in kidney fibrosis, we used an established mouse model for kidney fibrosis, unilateral ureteral obstruction (UUO) model in global and PT-specific CypD knockout (KO).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Global CypD KO blunted kidney fibrosis progression with inhibition of myofibroblast activation and collagen deposition. UUO-induced tubular atrophy was suppressed in kidneys of global CypD KO, but not tubular dilatation or apoptotic cell death. PT cell cycle arrest was highly increased in WT-UUO kidneys, but markedly attenuated in global CypD KO-UUO kidneys. The number of macrophages and neutrophils was less in UUO kidneys of global CypD KO than those of WT. The pro-inflammatory and fibrotic factors were all inhibited in global CypD KO. In line with those of global CypD KO, PT-specific CypD KO also blunted kidney fibrosis progression, along with less tubular atrophy, renal parenchymal loss, cell cycle arrest in PT and inflammation, indicating a critical role for PT CypD in fibrosis.

Conclusions: Collectively, our data demonstrate that CypD in PT is a critical factor contributing to kidney fibrosis in UUO, providing a new paradigm for mitochondria-targeted therapies of fibrotic diseases.

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PO2501
Reduction of Hnf4α Expression in CKD Accelerates Disease Progression
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Background: Renal mitochondrial dysfunction is a common feature of Chronic Kidney Disease (CKD) and is associated with cardiovascular disease. Hnf4α is highly expressed in proximal tubules and controls the expression of genes involved in various metabolic pathways. Mutations in Hnf4α are associated with mitochondrial defects. We tested the hypotheses that renal Hnf4α decline in CKD contributes to mitochondrial dysfunction, DKD and onset of cardiovascular outcomes and that Hnf4α reduction in CKD is result of hyperphosphatemia.

Methods: We confirmed Hnf4α expression was reduced in the kidneys of Col4α3−/− mice, model of progressive CKD. Next, we performed RNA sequencing (RNAseq) on kidneys collected from WT and Col4α3−/− mice to identify genes and molecular pathways altered by Hnf4α reduction in CKD. We treated mice with a continuous administration of Hnf4α antagonist (BI-6015, 3 mg/kg/day) for 8 weeks to study the effects of Hnf4α suppression on renal and cardiac functions. To further evaluate the role of Hnf4α reduction in CKD progression, we injected 300 mg/kg BI-6015 to Col4α3−/− mice for 5 days. We also generated WT and Col4α3−/− mice with a Hnf4α deletion in kidney proximal tubules (Hnf4αfl/fl and Col4α3−/−Hnf4αfl/fl). Finally, to demonstrate that hyperphosphatemia reduces Hnf4α expression in the kidney, we fed WT mice a control diet and a high phosphate diet (HPD) for 6 weeks.

Results: RNAseq of Col4α3−/− mice kidneys showed impaired molecular pathways regulated by Hnf4α, including increased mitochondrial dysfunction and reduced oxidative phosphorylation. Inhibition of Hnf4α in WT mice led to kidney interstitial fibrosis and left ventricular hypertrophy, while in Col4α3−/− mice a shorter administration of Hnf4α antagonist accelerated the decline in kidney function (+450% serum creatinine vs. Col4α3−/−;Crt mice), demonstrating the crucial role of Hnf4α in CKD progression. Similarly, Hnf4α deletion in proximal tubules impaired kidney function in WT mice and further worsened it in CKD animals. WT mice fed a HPD diet showed a 70% reduction in renal Hnf4α expression, suggesting that hyperphosphatemia contributes to renal Hnf4α suppression.

Conclusions: Our results suggest that Hnf4α is a master regulator of mitochondrial function and might represent a novel therapeutic target to improve renal and cardiovascular outcomes in CKD.

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PO2502
Wasp Homolog Associated with Membranes and Microtubules Is a Kidney Disease Risk Gene
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Background: Genome-wide association studies identified hundreds of risk variants that are associated with kidney function traits. More than 90% of these variants are located in non-coding region of the genome and therefore their target genes, target cell type and disease mechanism remain not known.

Methods: Here we used human kidney expression and methylation of quantitative trait (QTL and mQTL) information and complex computational integration to identify target cell types for genetic variants. We obtained mice with genetic loss of WHAMM. We induced acute kidney injury by cisplatin injection and chronic disease by folic acid. Kidney function was analyzed by serum creatinine and blood urea nitrogen, real time PCR, western blotting, and histology analyses. We cultured primary kidney tubule cells, in addition, autophagy was assessed by ph-LC3B, GFP-RFP plasmid and microtubules by incubation with microtubule-depolarizers.

Results: Using Bayesian colocalization, summary mendelian randomization, and transcriptome-wide association studies we prioritized WHAMM as a kidney disease risk gene. Risk variant rs12903411 was associated with higher WHAMM expression. WHAMM is an ATG7 complex activator protein that is associated with mitochondrial dynamics by utilizing microtubules. WHAMM heterozygosity and knock-out mice subjected to cisplatin and folic acid injury presented with improved kidney function (BUN, creatinine) and lower expression of injury markers (Kim1, N-gal) and fibrosis markers. Primary tubular cells with WHAMM loss showed increased autophagy flux compared to wild type. Furthermore, WHAMM heterozygous and knock-out mice and cells showed improved mitophagy and reduced expression of inflammatory markers such as IL-18 and TNFα. Finally, we found that WHAMM showed lower pyroptosis induction by cleaved caspase1 and gsdem D levels compared to WT mice in the folic acid model.

Conclusions: In summary, this study identified WHAMM as a new kidney disease risk gene.

Funding: NIDDK Support

PO2503
Autophagy Gene ATG7 Regulates Albumin Transcytosis in Renal Tubule Epithelial Cells
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Background: Receptor-mediated albumin transport in renal proximal tubule epithelial cells (PTECs) is important to control proteinuria. Autophagy is an evolutionarily conserved degradation pathway and its role in intracellular trafficking through interaction with the endocytic pathway has recently been highlighted. In this study, we determined whether autophagy regulates albumin transcytosis in PTECs and suppresses albumin-induced cytotoxicity.

Methods: Human tubular epithelial cell line (HK-2) was used for all experiments. The cells were exposed to 10 mg/ml BSA for 6 h or 24 h as required. For autophagy related 7 (ATG7) knockdown (KD), cells were transfected with ATG7 siRNA. The intracellular trafficking of FeRn was examined by biotin-labeled recycling assay. Immunofluorescence of FeRn and Rab6 and Rab11 was observed by confocal microscopy. The transcytosis of albumin in HK-2 was evaluated using FITC-HSA-based transcytosis assay. The release of IL-8 and KIM-1 caused by excess albumin were measured by ELISA, and mitochondrial damage was measured by MitotrackerCMXRos. Results: FeRn partially co-localized with autophagosomes. FeRn was accumulated and recycling of FeRn was attenuated in ATG7 KD cells. Colonizations of FeRn with Rab7-positive late endosome or Rab11-positive recycling endosomes were reduced in ATG7 KD cells. In ATG7 KD cells, albumin transcytosis was significantly reduced, and albumin accumulated in the cells. Exposure to excess albumin induced autophagic flux in HK-2. Consistently, excess albumin-induced mitochondrial damage is enhanced in ATG7 KD cells. The release of IL-8 and KIM-1 from ATG7 KD cells was increased in response to excess albumin.

Conclusions: In PTECs exposed to excess albumin, autophagy is decreased and intracellular transport of FeRn is impaired, resulting in decreased albumin transcytosis. The resulting accumulation of albumin induces cytotoxicity in tubules. Preventing dysfunctional autophagy in PTECs might be beneficial in the clinical management of nephropathies with proteinuria.

Funding: Government Support - Non-U.S.

PO2504
Leveraging High-Content Imaging Platforms for Drug Discovery
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Background: Disruption of the structure and function of the glomerular filtration barrier, leading to proteinuria, is a hallmark of several podocyteopathies. Efficacy in translatable in vitro models is a critical first step to develop new therapies. For example, free fatty acids such as palmitic acid and proline sulfinate are well characterized in vitro models to model DN and FSGS. However, these models are low throughput, making them unsuitable for target and compound screening.

Methods: We used immortalized murine podocytes and adapted the readouts of in vitro assays to a high content imaging (HCS) platform. Readouts in response to Palmitic Acid (PA) included: apoptosis and cell viability by annexinV and propidium iodide staining or MITT, mitochondrial membrane potential by JC-1 and Mitotracker Deep Red; and mitochondrial and cytosolic reactive oxygen species by MitoSOX and DCF. Actin cytoskeleton dynamics were assessed by quantification of actin aggregation and soluble F-actin. We monitored actin aggregation that was partially rescued by cyclosporin A, a positive control. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation, which is difficult to quantify.

Results: Podocyte apoptosis and cell death was comparable to the readout by FACS, but capacity was increased by at least 4x. We observed a dose-dependent, incremental change in mitochondrial ROS and membrane depolarization. Mitotracker Deep Red was less sensitive than other assays for PA injury. PS treatment resulted in loss of Synaptotagmin and increase of Phalloidin aggregation, and is usually assessed by confocal microscopy, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 parameters related to actin aggregation and soluble F-actin. We monitored actin aggregation that was partially rescued by cyclosporin A, a positive control.

Conclusions: We established a reliable and semi-automated high-content imaging platform, which will facilitate a better mechanistic understanding of podocyte injury, as well as drug discovery, including target validation and compound screening in podocytes.

Funding: Commercial Support - Goldfinch Bio
The eNOS–NO Pathway Attenuates the Progression of Age-Related Kidney Diseases via Suppression of CEBPβ-Associated Inflammaging

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Background: Chronic kidney disease (CKD) is a very common clinical problem in elderly patients and is associated with increased mortality. As life expectancy continues to improve worldwide, the incidence of comorbidities and risk factors, such as hypertension and diabetes, that predispose this population to a high burden of CKD is rising. Chronic inflammation (inflammaging) is also an important cause of age-related organ damage, such as kidney disease, and we hypothesized that endothelial dysfunction accelerates the process of age-related kidney injury.

Methods: We evaluated the anti-inflammatory effects of nitric oxide (NO) as an endothelial function in bone marrow–derived macrophages (BMDM) using in vitro experiments. BMDM derived from Wild Type (C57BL/6); WT) were stimulated through NLPR3 inflammasome activation using LPS-ATP, and the IL-1β secretion was examined. To determine the importance of inflammasome activation in age-related kidney diseases, we used mice deficient in apoptosis-associated speck-like protein containing CARD (ASC)—which is an essential molecule for inflammasome activation—in vivo. We evaluated those mice (ASCKO), eNOS knockout (eNOSKO) mice, and eNOS-ASC double-knockout mice (eNOS-ASC-DKO).

Results: S-nitrosoglutathione (GSNO) attenuated the NLPR3 inflammasome activation that followed treatment with LPS-ATP. This indicates that NO directly inhibits NLPR3 inflammasome activation. GSNO also decreased the expression of inflammasome-related genes. To investigate the detailed mechanisms (epigenetic regulation), we performed ATAC-seq using BMDM. The binding region of the transcription factor C/EBP was significantly closed in the LPS+GSNO condition compared with the LPS condition. Recently, it has been reported that C/EBP is associated with the NLPR3 inflammasome and is activated in aging kidneys. These mice were sacrificed at 15 months of age; the glomerular injury was found to be exacerbated, and serum Cr was elevated in the eNOSKO-15M, but not in the WT-15M. These changes were improved in the eNOS-ASC-DKO.

Conclusions: The eNOS–NO pathway ameliorated the progression of renal injury by regulating the inflammasome of the aging kidney. NO directly inhibits NLPR3 inflammasome activation via the suppression of CEBPβ activation.

PO2506

Symmetric Dimethylarginine Inhibits Renal Fibrosis in Obstructive Kidneys

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Background: Symmetric dimethylarginine (SDMA) is regarded as an independent cardiovascular risk factor in patients with chronic kidney diseases. Renal interstitial fibrosis is a common pathology of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. In this study, we investigated the role of SDMA in renal fibrosis and its underlining mechanisms.

Methods: Normal saline (NS) and SDMA (2.50 mol/kg) were administered into the kidney through the left ureter in a mouse model of unilateral ureteral obstruction (UUO). UUO was performed ATAC-seq using BMDM. The binding region of the transcription factor C/EBP was significantly closed in the LPS+GSNO condition compared with the LPS condition. Recently, it has been reported that C/EBP is associated with the NLPR3 inflammasome and is activated in aging kidneys. These mice were sacrificed at 15 months of age; the glomerular injury was found to be exacerbated, and serum Cr was elevated in the eNOSKO-15M, but not in the WT-15M. These changes were improved in the eNOS-ASC-DKO.

Results: We observed that intrarenal administration of SDMA attenuated renal fibrosis as shown by Masson staining and Western blotting analysis of the expression of fibrogenetic, collagen-I and α smooth muscle actin (αSMA). In parallel, SDMA dose-dependently reduced the expression of pro-fibrotic proteins in TGF-β-stimulated HK2 cells. Phosphorylation of Smad3 protein was analyzed in vivo and in vitro, which showed that SDMA inhibited phosphorylation of Smad3 in UUO kidneys and TGF-β-stimulated HK2 cells.

Conclusions: Thus, our data suggest that renal SDMA exerts direct anti-fibrotic effects in fibrotic kidneys probably through inhibition of Smad3 signaling pathway.

PO2507

Targeting ARG1+ Macrophages Slows the Progression of AKI to CKD

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Background: Recently, ARG1+ myeloid cells were defined as a new subgroup that express a large number of pro-inflammatory and pro-fibrotic genes. However, its function and clinical application in kidney disease has not yet been identified.

Methods: We clarified the source of ARG1+ macrophages via the bone marrow transplantation and the parabiosis, and constructed macrophage-specific ARG1 knockout mice (ARG1Δ/Δ). CX3CR1Δ/Δ) and CX3CR1Δ/Δ, DTR mice. Kidney samples were analyzed through 10X single-cell sequencing technology. The arginase inhibitor nor-NOHA and RNAi lentiviral vector of ARG1 were applied to ischemia-induced kidney injury.

Results: Most of the intra-renal ARG1+ macrophages were from bone marrow. Knocking down ARG1 in macrophages alleviated ischemia-induced AKI and the subsequent chronic fibrosis, and reduced the infiltration of macrophages in the kidney, while depletion of CX3CR1+ cells aggravated ischemia-induced renal injury. GSEA analysis indicated that the function of ARG1+ macrophages is highly enriched in the regulation of the release of inflammatory factors, activation of immune inflammatory response, and secretion of extracellular matrix. More biological macrophage ligand–mesenchymal receptor pairs expressed in ARG1+ macrophages between mesenchymal cells compared to ARG1- macrophages. Inhibiting ARG1 activity alleviated the proliferation of ARG1+ macrophages and reduced ischemia-induced renal fibrosis. The application of RNAi lentiviral vector of ARG1 via the tail vein injection alleviated the renal fibrosis, reduced ARG1 expression and macrophage infiltration.

Conclusions: ARG1+ macrophages accelerated the development of AKI to CKD by promoting inflammation response, activating fibroblasts and secreting extracellular matrix proteins. Inhibiting the activity or expression of ARG1 in macrophages alleviated IR-induced renal fibrosis.

PO2508

UBE-1099, a Novel Non-Covalent Keap1-Nrf2 Inhibitor, Protects Against Renal Ischemia-Reperfusion Injury via Nrf2 Activation

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Background: Patients with chronic kidney disease (CKD) showed a decline in renal function, as illustrated by glomerular filtration rate (GFR), as the disease progresses. A covalent KeLch-like ICH1-associated protein 1 (Keap1) - Nuclear factor erythroid 2-related factor 2 (Nrf2) inhibitor, bardoxolone methyl, has been reported to increase the estimated GFR in patients with advanced CKD. However, it is unclear how the Nrf2 activator improved GFR. Previous studies have shown that bardoxolone imidazolide suppresses renal tubular damage in a mouse model of unilateral ischemic reperfusion without constratal renal necroptosis (U-IR). In this study, we evaluated in detail the effect of a novel non-covalent Keap1-Nrf2 inhibitor UBE-1099 on U-IR model.

Methods: A fluorescence polarization-based (FP) assay and NADPH:quinone oxidoreductase 1 (NQO1) activity were evaluated in vitro. Activity-inhibitory and simultaneous Hepa1c1c7 hepatoma cell were used to investigate a non-covalent Keap1-Nrf2 inhibitor. U-IR model was established using 10 week old male C57BL/6 mice. These mice were orally administered either the inhibitor (30 mg/kg, 10 mL/kg, once a day) or vehicle for 14 days. Renal damage was then evaluated by histopathological analysis and measurement of GFR using a percutaneous GFR measurement system (MediBeacon, St. Louis, Missouri). Protein and mRNA expression in the whole kidney were assessed by Western blot analysis and real-time PCR, respectively.

Results: UBE-1099 directly inhibited Keap1-Nrf2 interaction as assessed by the FP assay, and induced NQO1 enzyme activity at Hepa1c1c7. UBE-1099 showed Nqo1 mRNA induction activity as well as bardoxolone imidazolide in the kidney of a normal mouse by single oral administration. Oral administration of UBE-1099 to U-IR model mice increased NQO1 protein and mRNA expression in the kidney and improved the atrophic pathology, including renal tubular damage. More surprisingly, UBE-1099 also showed an increasing trend in GFR in that model.

Conclusions: A novel non-covalent Keap1-Nrf2 inhibitor UBE-1099 improved the atrophic pathology and reduced tubular damage resulting from Nrf2 activation in U-IR model mice. UBE-1099 has been suggested to be a promising drug for renal diseases associated with oxidative stress.

PO2509

Peroxiredoxin 5 Regulates Cyst Growth and Ciliogenesis via Modulating Aurora A and Plk1 Stability and Wnt Signaling Activation

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Background: Peroxiredoxin 5 (Prdx5) is an antioxidant enzyme that catalyzes the reduction of H2O2 and alkyl hydroperoxide and plays a protective role in neurological and cardiovascular disorders. However, the role and mechanism of Prdx5 in autosomal dominant polycystic kidney disease (ADPKD) is unknown.

Methods: To investigate the role and mechanism of Prdx5 on cyst growth and ciliogenesis in ADPKD, we knocked down Prdx5 in mIMCD3 and RPE cells with shRNA and siRNA, and performed Western blot, qRT-PCR and immunostaining analysis in renal epithelial cells and tissues. A 3-dimensional cell culture system was used to evaluate the effect of Prdx5 knockdown on cyst growth.

Results: We found that Prdx5 was downregulated in cystic renal epithelial cells and tissues. Knockdown of Prdx5 resulted in: 1) abnormal centromere amplification and multipolar spindle formation in mIMCD3 cells; 2) the upregulation of Polo-like kinase 1 (Plk1) and Aurora kinase A (AurA), essential in cell division and checkpoint regulation of mitosis; 3) the formation of cysts in a three-dimensional matrigel culture system using IMCD3 cells, which correlated with the phosphorylation and activation of PKD associated proliferation signaling, including ERK and mTOR; and 4) impaired primary cilia formation in mIMCD3 and RPE cells, which could be rescued by inhibition of Plk1 activity. In addition, we show that Prdx5 plays a crucial role in the regulation of Wnt signaling pathway activity in renal epithelial cells. Stimulation of Wnt5a ligand had no effect on ciliogenesis in Prdx5 knockdown cells. In contrast, stimulation of Wnt5a exacerbated ciliogenesis defect in Prdx5 knockdown cells. Consistent with Wnt5a activity on regulating primary cilia biogenesis, knockdown of Prdx5 decreased the recruitment of centriolar satellites PCM1 and CEP290, to the centrosome/basal body.
Conclusions: This is the first study to show that Prx5 regulates cyst formation and cell death via affecting the stability of different cells and decreasing the activation of associated signaling pathways. Prx5 could also control noncanonical Wnt5a-dependent regulation of ciliogenesis, a cascade of events that regulate the recruitment of centriolar satellites necessary for primary cilia biogenesis.

Funding: Other NIH Support - R01 DK084097 and NIH P30 DK106912

PO2510

Comparison of the Renal Effects of Heme-Dependent and Independent Soluble Guanylate Cyclase Targeting Drugs in 5/6 Nephrectomized Rats on High-Salt Diet

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Bayer AG, Pharmaceuticals R&D, Pharma Research Center, Wuppertal, Germany; 2Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China

Background: Soluble guanylate cyclase (sGC) targeting drugs were reported to have beneficial renal effects in chronic kidney disease (CKD). The sGC stimulators bind to reduced, heme-containing sGC, while sGC activators bind to heme-free sGC and their actions are heme-independent. Regarding renal outcomes, the potential differences between these two classes of drugs are unknown so far. This study aimed to provide a head-to-head comparison of the renal effects of BAY 41-8543 (sGC stimulator) and BAY 60-2770 (sGC activator) in 5/6 nephrectomized rats on high salt diet as a model of CKD.

Methods: Rats were allocated to the following groups: Sham + normal diet + placebo (PBO); 5/6Nx + 2% high salt diet (HSD) + PBO; 5/6Nx + HSD + Telmisartan (5mg/kg/day); 5/6Nx + HSD + BAY 60-2770 (1mg/kg/day); 5/6Nx + HSD + BAY 41-8543 (1mg/kg/day). The treatment period was 8 weeks.

Results: Blood pressure was significantly decreased by BAY 60-2770 and BAY 41-8543 versus placebo (-32.52±27.20 mmHg, p<0.001; -23.83±29.90 mmHg, p<0.001, respectively), which was also comparable to the effects of telmisartan (-24.24±31.90 mmHg, p<0.001). Plasma creatinine was not altered by any of the 3 drugs, however, renal fibrosis was significantly decreased by BAY 60-2770 (44.76%, p<0.05) and telmisartan (43.96%, p<0.05) versus placebo. On the other hand, BAY 41-8543 did not ameliorate renal fibrosis. RNA-sequencing in renal tissues revealed that 144 genes were differentially regulated among the groups. Interestingly, 23 genes including collagen type VI alpha (Col6a5) were exclusively regulated among the groups. Interestingly, 23 genes including collagen type VI alpha (Col6a5), phospholipase C Eta 1 (PLCE1) and claudin 19 (Cldn19) were exclusively differentially regulated by BAY 60-2770 and these genes might explain anti-fibrotic renal effects.

Conclusions: Only the sGC activator BAY60-2770 ameliorated renal fibrosis comparable to the gold-standard treatment of CKD with an ARB (telmisartan). These results suggest that sGC activators represent potential novel therapeutic interventions in CKD.

PO2511

In-Depth Proteomic Analysis to Identify the Cellular Proteins and Secretome of Human Tubular Epithelial Cells with Fibrotic Injury

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Background: Fibrosis is the major pathophysiology in the development of chronic kidney disease. While there are several proteomic studies to reveal the mechanism of renal fibrosis, the in-depth analysis which elucidate the repertoire of proteins expressed on cell or released into extracellular space are lacking.

Methods: To induce the fibrosis on kidney cells in stages, two different dose (1ng/ml and 2ng/ml) of TGFβ1 are treated on primary cultured human renal proximal convoluted tubule cells (PCTCs). For global proteome and secretome profiling, liquid chromatography-tandem mass spectrometry based quantitative proteomic analysis were performed on isolated TECs and their media, respectively.

Results: When comparing the cellular proteins expressed in control and in cells with fibrosis, we identified 4061 and 1344 differentially expressed proteins in low and high dose treated cells, respectively. And the DEPs in secretomes from low and high dose treated cells were 168 and 283, respectively. Then we identified overlapping 74 DEPs which showed significant difference in both cell and secretome analysis. Eleven proteins including NAMP1 and KRT18 were decreased in similar manner in both cell and secretome analysis, suggesting overall decrease in expression of these proteins with fibrosis. Seventeen proteins including STRAP and EIF3B were significantly decreased in cells while increased in secretome, representing the possible extracellular release of proteins with the response to fibrosis injury. There were 25 proteins including SERPINE1 and CTGF significantly elevated in both cell and secretome identified. And the other proteins including SERPINE2, CTSK, COL1A1, COL3A1, COL4A1, and CDH1 were upregulated in both cell and secretome.

Conclusions: We identified different protein expression changes in cells and secretomes following fibrotic injury. Further studies are needed to validate the pathophysiological role of these proteins on kidney tubulointerstitial fibrosis.

Funding: Commercial Support - Bayer AG

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO2514
Oxysterol-Binding Protein Like 7 in CKD
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Background: ATP-binding cassette transporter A1 (ABCA1)-mediated, cholesterol ester-induced podocyte injury plays a major role in the progression of glomerular disease and pharmacological inducers of ABCA1 (ABCA1i) are sufficient to partially rescue glomerular injury in proteinuric mice. Interestingly, these ABCA1i’s compete specifically with oxysterol binding to oxysterol-binding proteins (OSBP) like 7 (OSBP7), a member of a group of lipid-binding proteins involved in lipid transport between intracellular membranes. OSBPs are implicated in cholesterol transfer from the endoplasmic reticulum (ER) to the Golgi, in cholesterol efflux and in the regulation of ABCA1 expression. However, if OSBP7 is expressed in the liver and if it is involved in the preservation of ER function has not been explored.

Methods: In this study, we utilized podocytes and tissues obtained from wildtype and Col4a3−/− mice, an experimental model of CKD. siOSBP7 Podocytes and HEK293 cell lines were established using siRNA yielding these cells deficient in OSBP7. HEK cells do not express ABCA1 making them a valuable tool to study the ABCA1 independent effects of OSBP7. OSBP7 levels were determined from kidney cortex and isolated podocytes from WT and Col4a3−/− mice by western blot, immunohistochemistry, and RT-PCR. siOSBP7 podocytes and HEK cells were analyzed for changes in ER stress markers, reactive oxygen species (ROS), cytotoxicity, and apoptosis.

Results: OSBP7 is expressed in podocytes isolated from wildtype and Col4a3−/− mice, an experimental mouse model of chronic kidney disease. Western blot analysis revealed that OSBP7 protein levels are reduced in kidney cortex of Col4a3−/− mice. siRNA knockdown of OSBP7 in HEK 293 cells showed increased levels of ER stress, ROS, cytotoxicity, and apoptosis. Overexpression of OSBP7 in Col4a3−/− podocytes lead to a reduction in apoptosis levels further indicating a beneficial role of OSBP7 in podocytes.

Conclusions: This study represents the first time that OSBP7 has been implicated in CKD. OSBP7 deficiency in podocytes leads to ER stress and ultimately apoptosis suggesting that OSBP7 levels are beneficial to podocyte function. Future studies will address the role of OSBP7 in podocyte lipid trafficking in chronic kidney disease that may lead to the identification of novel therapeutic targets for the treatment of this prevalent and costly disease.

Funding: NIDDK Support

PO2525
Determinants of Serum Phosphate Concentration in CKD
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Background: The mean age (SD) of the cohort was 73 (10) years. 96% were male, 74% were black, 48% had diabetes. In a steady state, E/P-Cr rises as P intake rises or Cr falls. TRP/Cr, calculated as SP – E/P-Cr, is hormonally regulated. We aimed to analyze the evolution of SP and its determinants over CKD stages G1-G5 (diabetes excluded).

Methods: This was a retrospective study involving 200 US veterans followed in the nephrology clinic of the Albany VAMC from 1/2020 to 4/2021. CKD stages were based on 4-variable MDRD eGFR. There were 293 simultaneous random measurements of SP, UP, Scr, Ucr, PTH, and eGFR. Means of these parameters were plotted against CKD stages G1-G5.

Results: The mean age (SD) of the cohort was 73 (10) years. 96% were male, and 48% had diabetes. In comparison to stages G1-G2, E/P-Cr rose and TRP/Cr fell significantly starting at stage G3b (Figure). EP/Cr correlated with eGFR (R² = 0.28, p < 0.001), but TRP/Cr and SP did not. SP correlated with EP/Cr (R²=0.24, p<0.001) and TRP/Cr (R²=0.36, p<0.001). PTH correlated with EP/Cr (R²=0.32, p<0.001) and TRP/Cr correlated with PTH (R²=0.10, p< 0.001).

Conclusions: EP/Cr rises consistently as eGFR falls. At stage G3b, the decrement in TRP/Cr equals the increment in EP/Cr, and SP remains stable. In stages G4 and G5, the rise in E/P-Cr is greater than the fall in TRP/Cr, and SP ascends accordingly. As eGFR declines, PTH rises, but its apparent effect on TRP/Cr is blunted. As CKD progresses, maintenance of stable SP depends primarily on reduction of intestinal P absorption.

Funding: Veterans Affairs Support

PO2516
Tubular Urate Controls Intracellular Lactate in the Proximal Tubule with Implications for CKD
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Background: Alterations in cell metabolism in the proximal tubule are a recognized component in the initiation and progression of chronic kidney disease (CKD). Previously, a mouse model of hyperuricemia revealed elevated serum urate was associated with hyperglycemia and altered expression of key mitochondrial complex I and complex IV genes in the kidney, changes implicated in human CKD. Further, a recent animal showed that blockade of proximal tubule urate transporter, URAT1, in conjunction with urate lowering therapy, slowed the progression of CKD as defined by change in albuminuria. Here, we focused on the role of renal urate handling in controlling the intracellular levels of lactate, a key metabolite and substrate of cellular respiration. Lactate is a substrate of URAT1 (SLC22A12) moving in from the apical entry of urate from the renal tubule lumen. We hypothesized that increased extracellular urate would promote the secretion of lactate and lower intracellular levels.

Methods: We used cultured primary normal human cortical renal epithelial cells (NHCRE) and a new hyperuricemia mouse model, produced by the inducible inactivation of the uricase gene, Uox, to explore the relationship between urate and CKD.

Results: In NHCRE cells we found that increasing the extracellular urate to 500µM significantly lowered intracellular lactate with high (4.5g/l) or reduced levels of glucose (1g/l) in the culture media, and that additional extracellular lactate could rescue intracellular levels. Further, the application of probenecid, a general anion transporter blocker with affinity for URAT1 abolishes the effects of extracellular urate on lactate levels, though probenecid alone has no effect. Finally, we sought to confirm the relationship between urate and lactate handling in the mammalian nephron. In the inducible Uox knockout hyperuricemia mouse model we found the increased plasma urate and resulting increased urinary urate excretion was associated with an increased urinary lactate excretion as well as a significant increase in the fractional excretion of lactate.

Conclusions: We conclude that increased tubular urate alters intracellular lactate levels, which potentially alters cellular respiration in the proximal tubule and affects kidney disease progression.

Funding: NIDDK Support, Commercial Support - AstraZeneca

PO2517
A Severe Case of Secondary Hyperoxaluria Successfully Treated
Veronica Zamora-Olivencia, Cybele Ghasseim. McGaw Medical Center of Northwestern University, Chicago, IL.

Introduction: Bariatric Surgery for the treatment of obesity is categorized as either restrictive or malabsorptive. Malabsorptive procedures are often used for long lasting weight loss in morbidly obese patients. The Bilopancreatic Diversion and Duodenal Switch (BPD/DS) is preferred for patients with more severe comorbidities as it provides best durability, minimal dumping syndrome and less dietary restriction. Malabsorption weight loss surgeries have been associated with AKI, CKD, nephrolithiasis and metabolic and nutritional derangements. Here we report a patient with history of BPD/DS with CKD due to hyperoxaluria.

Case Description: A 70-year-old female with history of morbid obesity since childhood, who was post BPD/DS surgery in 2004 with persistent hyperoxalemia, severe osteoporosis and newly recognized chronic kidney disease (CKD) was referred for nephrology consultation. Serum creatinine pre-surgery was 0.9. Her eGFR at the time of referral was 42cc/min and her urinalysis was without proteinuria. Renal Ultrasound was without nephrolithiasis. As part of her work up, a 24-hour urine collection for oxalate was obtained and revealed severe oxaluria at 160mg/day. Patient’s medications included 4 grams a day of Calcium Citrate along with multiple other supplements. Patient admitted to non-compliance with her calcium supplements. After two months of strict compliance
with low oxalate diet and calcium supplements a 24-hour urine collection showed improvement of oxaluria to 62 mg/day. Her renal function remained stable.

**Discussion:** Patients who undergo malabsorptive weight loss surgery are at risk for AKI, CKD and nephrolithiasis from hyperoxaluria. Kidney damage can continue years after the surgical procedure. Treatment involves low oxalate diet and aggressive oxalate binding with use of calcium supplements. Bariatric surgery reversal is the definitive treatment if conservative management fails. Bariatric patients should be referred promptly to a nephrologist if change in renal function is noted.

**PO2518**

**Increasing Acid Retention with Progressive GFR Decline Is Associated with Decreasing Urine Ammonium Excretion**

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**Background:** Our laboratory showed that acid (H+) retention without metabolic acidosis increased as GFR declined while plasma total CO₂ (PTCO₂) remained within normal ranges (AJP 314: F985, 2018) but the mechanisms for this potential accelerator of GFR decline were not explored. We now examine if changes in urine net acid excretion (UNAE) or its components associated with changes in H+ retention in longitudinally followed patients with CKD 2 (eGFR 60-89 ml/min/1.73 m²) without metabolic acidosis.

**Methods:** One hundred twenty macroadbuminic, non-diabetic patients with CKD 2 (eGFR=75±6.1 ml/min/1.73 m²), 40 treated with 0.5 mEq/kg bw NaHCO₃, 40 with 0.5 mEq/kg NaCl, and 40 with usual care (UC) were evaluated annually for 5 years. We assessed H+ retention by comparing observed to expected increase in plasma pH (H+) in response to administered HO₂⁻ (HCO₃⁻) bolus (0.5 mEq/Kg bw), assuming 50% body weight HCO₃⁻ space of distribution. Specifically, H+ retention = (retained HO₂⁻/0.5 x body weight) – observed increase in plasma [HCO₃⁻]. We measured 8-hour urine NAE as the sum of ammonium (8h UNH), titratable acidity (8h UTAV) and bicarbonate (UHCO₃).

**Results:** Although 5-year vs. baseline H+ retention was higher in UC (19.2±10.2 vs. 17.4±9.7 mmol, p<0.05) and NaCl (23.2±13.8 vs. 19.2±16.4 mmol, p<0.05) but was lower in NaHCO₃ (16.8±12.8 vs. 18.1±14.6 mmol, p<0.05), 5-year vs. baseline 8h UNAE was not different for any group and was not different among groups at baseline or at 5 years. Nevertheless, longitudinal change in 8h UNH, V was inversely associated with change in H+ retention for UC (p<0.01, R²=0.82), NaCl (p<0.01, R²=0.71), and NaHCO₃ (p<0.01, R²=0.20). Combining all three groups, the change in 8h UNH, V was also inversely associated with the change in H+ retention (p<0.01, R²=0.48) but the longitudinal change in 8h UTAV was directly associated with change in H+ retention (p<0.01, R²=0.19).

**Conclusions:** These longitudinal data support that less ability to maintain UNH, V as eGFR declines contributes to worsening H+ retention, despite maintenance of overall UNAE. Further studies will determine reasons for individual variability in UNH, V with progressive eGFR decline and the apparent greater importance of UNH, V than greater UTAV in avoiding increasing H+ retention.

**Funding:** Private Foundation Support

**PO2519**

Kidney Function and Renin-Angiotensin-Aldosterone System in Hypouricemia

Lashodva V. Dissanayake, Adrian P. Zietara, Vladislav Levcenkov, Oleg Palygin, Alexander Staruschenko. Medical College of Wisconsin, Milwaukee, WI.

**Background:** Uric acid (UA), the end-product of human purine catabolism, is produced using xanthine dehydrogenase (XDH) and xanthine oxidase enzymes. Both enzymes are encoded by the XDH gene. Disruption of UA homeostasis has been implicated in chronic kidney disease for many years. However, the mechanisms behind the correlation remain unclear. Increased level of UA (hyperuricemia) has been shown to activate the intrarenal Renin-Angiotensin-Aldosterone system (RAAS) in many studies. RAAS in plasma

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**Methods:** Zucker Rats Fed with High-Sodium Diet

Kalvani Kulkarni, Tahir Hussain, Sanket N. Patel. University of Houston System, Houston, TX.

**Background:** The appearance of protein in the urine (i.e. proteinuria) is a function of the glomerular filtration rate of protein and the reabsorption of protein from the post-glomerular filtrate by the endocytic receptors, megalin and cubilin, localized in the renal proximal tubules. We have shown that treatment with the angiotensin-II type 2 receptor (AT₂R) agonist C21 for 2 weeks reduces proteinuria in obese Zucker rats (OZR) fed HSD. The consumption of sodium-rich diet (HSD) can acutely precipitate proteinuria which is a risk factor and indicator of kidney injury. Therefore, the objective of this study was to identify the acute and chronic mechanism that may have been involved in proteinuria upon consumption of HSD and to identify the anti-proteinuric mechanism upon AT₂R activation in obesity.

**Methods:** Male OZR were treated acutely (2 days) or chronically (14 days) without or with AT₂R agonist C21 (1mg/kg/day) while fed with normal salt diet NSD (0.4%) or HSD (4%).

**Results:** The effects of HSD feeding on the expression of endocytic receptor megalin was biphasic. The HSD feeding for 2 days decreased, but for 14 days, increased megalin expression (p<0.05 vs. OZR). However, at 2- and 14-days, HSD feeding caused significant proteinuria (p<0.05 vs. OZR). The expression of cubulin remain unaffected. The AT₂R agonist treatment significantly prevented the HSD-associated changes in the expression of megalin at 2-days and 14-days, and prevented the onset of proteinuria. The expression of glomerular proteins, nephrin and podocin, which are part of the renal filtration apparatus, in the kidney cortex remains unaffected at 2-days, which suggest that glomerular filtration of protein due to the loss of these glomerular proteins, per se, is not affected by HSD intake and that altered tubular reabsorption is involved in the initiation of early kidney injury.

**Conclusions:** Collectively, these data suggest that AT₂R activation protects against HSD induced proteinuria in obese rats by preventing the early loss of endocytic receptor megalin.

**Funding:** NIDDK Support
Regional Citrate and Systemic Heparin Are Adequate to Maintain CRRT Half-Life for COVID-19 Patients on CRRT

Cassandra Chiao, Hilary Faust, Tripti Singh. University of Wisconsin-Madison, Madison, WI.

Background: The aim of our study is to compare cloting of CRRT filters in patients with COVID-19-associated AKI vs. septic shock-associated AKI.

Methods: Retrospective single center study of adult patients with COVID-19 infection compared to those with septic shock admitted to the ICU at a tertiary university hospital April-October 2020. We used independent t-test and chi square test to determine statistical significance of CRRT filter clotting and related factors in COVID-19 patients compared with septic shock patients in the ICU. Time to event data was analyzed with Kaplan-Meier curves. Analyses were performed on Microsoft Excel and MedCalc.

Results: A total of 27 ICU patients with AKI requiring CRRT were included in the study, 13 with COVID-19 infection and 14 with septic shock. The mean half-life of CRRT hemofilter was similar in COVID-19 patients compared to non-COVID-19 patients (27.4 hours ± 27.5 hours, p=0.79). The number of CRRT hemofilter changes per patient were also similar in both groups (0.6 filter changes per day, p=0.84) (fig. 1). However, significantly more patients with COVID-19 were on systemic heparin compared to the non-COVID-19 patients (69% vs 13%, p= 0.02) (fig. 2).

Conclusions: We found that COVID-19 patients with AKI requiring CRRT had similar CRRT hemofilter half-life compared with sepsis-associated AKI patients with use of regional citrate anticoagulation and systemic heparin use. Further studies are needed to find which methods of anticoagulation is optimal in patients with COVID-19 infection with AKI requiring CRRT.

Kidney Disease in the Aftermath of COVID-19 Infection

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Introduction: COVID-19-associated nephropathy (COVAN) is a known, but potentially missed cause of AKI. We present a case of COVAN presenting with a severe AKI in a previously healthy patient.

Case Description: A 48-year-old African American male with no known past medical history and a recent COVID-19 infection presented with hypertension and lower extremity edema. Initial work-up showed BUN 60, Cr 4.8. Urinalysis was significant for proteinuria. Urine protein to Cr ratio was 1.4. Renal ultrasound did not show any hydronephrosis. Initial management included blood pressure control and intravenous hydration, and his Cr downtended to 3.1. Of note, his Cr was 1.2 two weeks prior to admission. Given his acute renal failure and significant proteinuria, a renal biopsy was obtained which showed collapsing FSGS consistent with COVAN.

Discussion: Glomerular disease is a known complication of COVID-19. The most distinct presentation is the collapsing FSGS seen in this case (Image 1). This has primarily been reported in patients of African descent, specifically those with high-risk APOL1 genotypes. Patients may recover kidney function, but some may also develop CKD. One recent study found that the hospitalization of this patient’s Cr was 4.3 and we suspect that he will likely have significant CKD. COVAN can be a difficult diagnosis to make. Proteinuria can often be attributed to common co-morbidities, therefore confounding its diagnosis. The timing also complicates the diagnosis, as in our patient who presented a week after his COVID-19 symptoms resolved. With COVID-19 vaccines, perhaps COVAN may become more common.

Discussion: Glomerular disease is a known complication of COVID-19. The most distinct presentation is the collapsing FSGS seen in this case (Image 1). This has primarily been reported in patients of African descent, specifically those with high-risk APOL1 genotypes. Patients may recover kidney function, but some may also develop CKD. One recent study found that the hospitalization of this patient’s Cr was 4.3 and we suspect that he will likely have significant CKD. COVAN can be a difficult diagnosis to make. Proteinuria can often be attributed to common co-morbidities, therefore confounding its diagnosis. The timing also complicates the diagnosis, as in our patient who presented a week after his COVID-19 symptoms resolved. With COVID-19 vaccines, perhaps COVAN may become more common.

Treatment Outcome of New-Onset Collapsing Focal Segmental Glomerulosclerosis in a Patient with COVID-19
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Introduction: COVID-19 has been shown to cause acute kidney injury (AKI) in as high as 46% of hospitalized patients. This case describes a patient who developed an AKI during her admission for COVID-19 pneumonia and was found to have collapsing focal segmental glomerulosclerosis (FSGS). Several cases of FSGS associated with COVID-19 have been described in the literature with varying outcomes. Unfortunately, the patient described in this case has not had significant recovery despite months of high-dose prednisone.

Case Description: A 57-year-old African-American female with a history of diabetes mellitus type 2, hypertension, and small cell lung cancer was admitted for intractable vomiting and found to be positive for COVID-19. Despite no history of kidney disease, patient developed an AKI over the first few days of hospitalization with creatinine 1.96 mg/dL, (which continued to rise) from baseline 0.7-0.8 mg/dL. Urinalysis demonstrated new onset high urine protein/creatinine ratio greater than 12 g/g. Renal biopsy demonstrated collapse of the glomerular tufts and associated hypertrophic podocytes, consistent with collapsing FSGS. No significant immunofluorescence staining was seen. Other serologies were negative, including HIV. Following discharge, she was started on prednisone 60mg daily. Despite several months of prednisone, patient’s creatinine remained elevated, mostly in the range of 2.5-3.5 mg/dL, never returning to baseline. She continued to have nephrotic range proteinuria and no response to prednisone therapy was noted.

Discussion: As COVID-19 is a new and rapidly evolving disease, extrapulmonary disease is being newly identified, necessitating development of effective treatment strategies. Many of the cases that described collapsing FSGS in COVID-19 patients required initiation of dialysis. The patient in this case recovered from the respiratory onset of COVID-19, but continued to have impaired renal function despite several months of treatment. This case demonstrates prednisone failure for our patient, and further study is needed to determine more effective treatment regimens.

PUB006

Safety and Efficacy of Bedside Insertion of Tunneled Hemodialysis Catheters in Critically Ill Patients with COVID-19
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Background: Critically ill patients with coronavirus disease-2019 (COVID-19) and kidney dysfunction often require tunneled hemodialysis catheter (TDC) placement for kidney replacement therapy (KRT), typically under fluoroscopic guidance to minimize catheter-related complications. This entails transportation of patients outside the intensive care unit (ICU) to a fluoroscopy suite, which may potentially expose many healthcare workers and other health care providers to COVID-19. One potential strategy to mitigate the risk of viral transmission is to insert TDCs at the bedside, using ultrasound (US) and anatomic landmarks only, without fluoroscopic guidance.

Methods: We reviewed all COVID-19 patients in the ICU who underwent right internal jugular (RIJ) TDC insertion at the bedside utilizing anatomic landmarks under US guidance between April-December 2020. Outcomes included procedural complications such as bleeding, arterial puncture, venous air embolism, arrhythmias, pneumothorax, hemothorax and catheter tip malposition. TDC insertion was considered successful if the catheter was able to achieve blood flow sufficient to perform a single hemodialysis treatment.

Results: We collected data on 25 patients with COVID-19 who had RIJ TDCs placed at the bedside, 10 of whom underwent simultaneous insertion of small-bore (5 Fr) RIJ tunneled central venous catheters (T-CVC). The median age and body mass index of the cohort were 62 years (interquartile range [IQR]: 55-70) and 28.8 kg/m² (IQR:25.2-33.2) respectively; comorbid conditions included chronic kidney disease (n=14), diabetes mellitus (n=12) and hypertension (n=18). Continuous veno-venous hemodialysis was the KRT modality employed in all patients. A median catheter blood flow rate of 200 ml/min (IQR:200-200) was achieved in all patients without any deviation from the dialysis prescription. No catheter related complications were observed and none of the catheter tip sizes were mal-positioned on post-insertion chest radiography images.

Conclusions: bedside RIJ TDC placement in COVID-19 patients, using US and anatomic landmarks without fluoroscopic guidance, may potentially reduce the risk of COVID-19 transmission amongst health care workers without compromising patient safety or catheter function. Continuous venous-venous hemodialysis may also be safely accomplished and further help limit personnel exposure to COVID-19.

Irreversible Damage from a Pandemic Outbreak: A Rarely Described Case Report
Maria Teresa Furtado, Patricia A. Domingues, Ana D. Pidcada, Catarina A. Gonçalves, Patricia Valério. Hospital de Sao Bernardo, Setubal, Portugal.

Introduction: Renal cortical necrosis (RCN) is a rare cause of acute kidney injury (AKI) in developed countries with frequency of 1.9%-2% of all patients with AKI. Drugs especially non-steroidal anti-inflammatory drugs (NSAIDs) are very rarely described to cause cortical necrosis. It happens due to permanent occlusion of afferent arterioles and interlobular arteries in the cortical vasculature, either by prolonged vasospasm or primary vascular damage with thrombosis.

Case Description: We present the case of a 20-year-old black man who was admitted to the hospital due to abdominal pain and decreased urine output. He had been symptomatic with severe toothache due to a dental abscess. Since it happened during the pandemic outbreak of COVID-19 he was unable to contact any dentist and he was given regular oral paracetamol and ibuprofen in doses he could not quantify (ibuprofen exceeded 600 mg every 8 hours daily in a week). Initial laboratory tests revealed anemia (Hb 11 g/dL), slight increase in inflammatory parameters and acute renal failure (sCreatinine 12.7 mg/dL., sUrea 109 mg/dL) and a urine protein-to-creatinine ratio of 1.8 g/g. Renal ultrasound excluded obstruction. Viral serologies were negative, clonal gammopathies were excluded, autoimmune study and serum complement levels were normal. Blood and urinary cultures were also negative. He underwent tooth extraction and completed 10 days of amoxicillin-clavulanate and metronidazole with resolution of...
infection. Despite proper fluid replacement the patient showed no clinical improvement and presented with anuria, so hemodialysis was started. Abdominal and pelvic CT scan showed no positive findings. A renal biopsy was obtained showing extensive cortical necrosis. At that moment we concluded renal cortical necrosis probably secondary to NSAIDs intoxication. Unfortunately, the patient did not recover and became dependent on renal replacement therapy.

Discussion: This case illustrates the need to be aware of the effect of NSAIDs. Despite being readily available, a subset of individual is susceptible to serious renal toxicity and caution should be exercised when these drugs are used. Our patient presented with bilateral renal cortical necrosis with irreversible renal failure secondary to prolonged use of over-the-counter NSAIDs in the setting of pandemic outbreak of COVID-19.

PUB008
Challenges in Conducting a Clinical Trial During the COVID-19 Pandemic
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Background: The COVID-19 pandemic has caused a global upheaval in daily life, economics, clinical care, and research. We report challenges faced and addressed based on our experiences conducting an NIH-funded randomized controlled clinical trial during the pandemic.

Methods: Combination of Novel Therapies for CKD Comorbid Depression (CONCORD) is an ongoing multi-center randomized trial comparing two novel 16-week treatment strategies for depression, vs. a placebo and attention control group, in 200 patients with stages 3-5 non-dialysis CKD. One strategy is to deliver bupropion, an antidepressant drug for 8 weeks, with augmentation to combination bupropion and behavioral activation teletherapy (BAT) for an additional 8 weeks if depression did not remit. The second strategy is to deliver BAT for the first 8 weeks, with addition of bupropion for 8 more weeks for non-remitters.

Results: Since October 2020 to-date, 690 patients were screened at the University of Texas Southwestern, Dallas, and at the University of Washington, Seattle, of whom 151 (21%) met the screening cutoff for depression. Despite the ongoing pandemic, this percentage was similar to previously reported rates for CKD patients. Thirty-one (80%) of the 39 target to-date were randomized, and 22 (71%) have completed the trial. Only 2 exited before 16 weeks. The national shift away from in-person visits to telehealth slowed screening from outpatient clinics. A lower number of screening surveys were conducted due to unavailability of patients via telephone. Because CKD patients have a high burden of healthcare contact and barriers to accessing in-person care, CONCORD was designed prior to COVID-19 to use teletherapy instead of in-person visits to minimize burden. Telehealth intervention delivery has been especially beneficial in minimizing in-person contact during the pandemic. Blinded assessments of primary outcome were also conducted by computer-assisted telephone interview. Thus, the protocol allowed minimization of in-person visits, which were further decreased from every 4 to every 8 weeks only for phlebotomy and drug dispensation.

Conclusions: Despite challenges posed by COVID-19, CONCORD successfully upped its enrollment rate, due to perseverance of staff, use of teletherapy to minimize in-person visits, and patients’ willingness to participate.

PUB009
Mortality and Evolution Between Community and Hospital-Acquired COVID-AKI (CA-AKI and HA-AKI)
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Background: Differences between HA-AKI and CA-AKI are not well established. We aimed to address these differences.

Methods: Retrospective cohort. We included 877 patients hospitalized with COVID-19 at two hospitals in Mexico. Primary outcome was all-cause mortality at 28 days compared between COVID with CA-AKI and HA-AKI. Secondary outcomes included the need for RRT, and risk factors associated with the development of CA-AKI and HA-AKI.

Results: A total 33.7% developed AKI. CA-AKI occurred in 59.9% and HA-AKI occurred in 40.1%. Patients with CA-AKI had more comorbidities than those with HA-AKI. Patients’ survival with CA-AKI it was 75.4%, and with HA-AKI 69.6%. Age > 60 years (OR 1.12), COVID severity (OR 1.09), mechanical ventilator (OR 1.67), and HA-AKI 3 (OR 1.16) increase mortality. The presence of CKD (OR 1.48), serum lymphocytes < 1000 µL (OR 1.03), the need for mechanical ventilator (OR 1.06), and CA-AKI stage 3 (OR 1.37) were the only variables associated with a KRT start.

Conclusions: We found that COVID complicated by CA-AKI have more comorbidities and worse biochemical parameters than HA-AKI patients, but despite these differences, their probability of dying is similar.

PUB010
Predictors of Short- and Longer-Term Mortality After COVID-19 Presentation Among Dialysis Patients in the Americas
Adrian M. Guinsburg,1 Yue Jiao,2 Maria Inés Diaz Bessone,3 Caitlin Monaghan,2 Michael A. Kraus,4 Peter Kotanko,1,3 Jeffrey L. Hymes,2 John W. Larkin,2 Len A. Usvyat,2 Robert J. Kossmann,5 Juan Carlos Berbessi,4 Franklin W. Maddux,6 Fresenius Medical Care Latin America, Rio de Janeiro, Brazil; 3Fresenius Medical Care, Global Medical Office, Waltham, MA; 1Renal Research Institute, New York, NY; 4Fresenius Medical Care North America, Waltham, MA; 5Icahn School of Medicine at Mount Sinai, New York, NY; 6Fresenius Medical Care AG und Co KGaA, Bad Homburg, Germany.

Background: We aimed to build machine learning (ML) models to understand the predictors of short- and longer-term mortality among hemodialysis (HD) patients affected by COVID-19 in four countries in the Americas.

Methods: We used data from adult HD patients treated at regional institutions of a global provider in Latin (LATAM) & North America (NA) who had COVID-19. We used data on 96 variables from Jul-2019 through Dec-2020 to develop XGBoost models (60%:20%:20% random split for training, validation, & testing) to predict the likelihood of death in 0-14, 15-30, >30 days after COVID-19 presentation, and identify importance of predictors. Models were developed in a side-by-side manner and used same programming for datasets in LATAM (Argentina, Columbia, Ecuador) & NA (United States) countries.
Results: Among HD patients with COVID-19 in LATAM (n=12,121) and NA (n=21,624), 15.8% and 7.3% died within 0-14 days, 8.2% and 4.6% died within 15-30 days, and 4.8% and 6.6% died >30 days after presentation, respectively. Models in LATAM & NA had area under curve (AUC) in testing datasets of 0.64 & 0.70 for death within 30 days, and 4.8% and 8.6% died >30 days after presentation, respectively. The top 15 predictors and their AUCs were similar across models. Top predictors of death 15-30 days were higher pre-HD weight and post-HD systolic blood pressure (SBP) in LATAM, and same as 0-14 days in NA. Top predictors after >30 days were diabetes and higher pre-HD SBP in LATAM, and higher age and lower weight in NA.

Conclusions: Profiles of mortality in HD patients after COVID-19 were distinct in LATAM & NA. Mortality more often occurred within 0-14 or 15-30 days after COVID-19 in LATAM versus NA. About 5% to 9% of COVID-19 patients died >30 days after presentation. Risk factors of mortality for both periods were pre-HD weight and SBP, and for the later periods after COVID-19, albeit when considering top 15 predictors similarities exist. Comorbidities, demographics, weight, and BP appear risk factors for death after presentation. Use of underexplored follow-up timeframes along with ML modeling techniques that account for collinearity and missingsness provide novel insights related to mortality in COVID-19.

Funding: Commercial Support - Fresenius Medical Care

PUB011
SARS-CoV-2 Breakthrough Infection in a Fully Vaccinated Hemodialysis Patient
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Introduction: End-stage kidney disease (ESKD) is associated with immunosuppression manifesting as both increased infection rates & impaired vaccine immunoresponsiveness. Nonetheless, COVID-19 vaccines have proven highly effective in dialysis-dependent ESKD patients, with reported seroconversion rates as high as ~96%. Herein, we describe a case of breakthrough SARS-CoV-2 infection in a fully-vaccinated hemodialysis patient.

Case Description: A 69 year-old white male with dialysis-dependent ESKD presented for routine rural in-center hemodialysis with a new intermittent nonproductive cough following known COVID-19 exposure. He tested positive for COVID-19 via both rapid antigen testing & RT-PCR despite full mRNA-1273/Moderna SARS-CoV-2 vaccination ~2 mo prior, & was admitted for inpatient management pending availability of isolated outpatient dialysis. He was afebrile, normoxemic, & clinically stable at presentation & throughout his subsequent hospital course. Following 10 d of uneventful isolation, during which he received thrice-weekly hemodialysis but no COVID-19-antibodies. To our knowledge, there are no reported cases of circulating PLA2R antibodies and occurs rarely in patients with possible secondary MN. PLA2R positivity on renal biopsy is a strong indicator for PLA2R seropositive MN. PLA2R positivity on renal biopsy is a strong indicator for PLA2R seropositive MN and occurs rarely in patients with possible secondary MN. PLA2R positivity on renal biopsy is a strong indicator for PLA2R seropositive MN and occurs rarely in patients with possible secondary MN.

Discussion: Seropositive but biopsy-negative PLA2R associated MN is uncommon, and occurs rarely in patients with possible secondary MN. PLA2R positivity on renal biopsy has been reported in viral hepatitis and some cases had circulating serum PLA2R antibodies. To our knowledge, there are no reported cases of circulating PLA2R antibodies with COVID-19 infection. Our case illustrates the diagnostic and management challenges of MN in the era of widespread COVID-19 infection. Clinical course and PLA2R antibody titres remain useful guides for consideration of immunosuppressive treatment.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

769
PUB014

Impact of COVID-19 on Kidney Transplantation
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Background: Detrimental impact of COVID-19 on renal function unraveled over time. Nephrology community was in a dilemma whether transplantation should continue under such circumstances. We investigated which States within the US continued to perform kidney transplantation despite such odds.

Methods: Retrospective data from Organ Procurement and Transplantation Network (OPTN) regions for kidney transplant alone (KTA) performed across the US from 2019 to 2020, reflecting the peak of the first wave of COVID-19 pandemic were analyzed. To address whether the COVID-19 had an impact on transplanted kidneys, we analyzed graft survival at 3- and 6-months post-transplant during that era. We further investigated the statewide variation of KTA in both deceased donor (DD) transplants and living donor (LD) transplants.

Results: There was a 3.1% decrease in KTA from 2019 to 2020 (22,429 to 21,731). There was an overall trend of a decrease in number of transplants across all states with a peak decline in March-April 2019 era and rebound in May 2019 onwards. Statewide regional decline or variation of DD KTA was most significant in region 9 (NY, Vermont) while regions 4 (Oklahoma and Texas) continued to perform transplants unabated. In 2019, 30.6% of KTA were from DD while in 2020 the rate decreased to 24.1%. The decrease of DD transplants increased from 15,562 to 16,497 in 2020. Overall, 3-month graft survival was significantly negatively impacted for DD KTA performed between February and May. The decrease in KTA in the southern regions was less compared to the northeastern regions.

Conclusions: The COVID-19 pandemic had a major impact on kidney transplantation with a significant reduction within all OPTN regions. While LD transplantation could presumably be rescheduled, DD organs must be procured immediately, or they are lost. Therefore, the number of DD transplants decreased initially between March and May but recovered afterwards. Transplanted kidneys during COVID-19 first wave pandemic era performed reasonably well but with an increased rate of injury and rejection.

PUB015

SARS-CoV-2 Antibody Dynamics in Chronic Hemodialysis Patients
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Background: Data on the persistence of COVID-19 antibodies against SARS-CoV-2 in maintenance hemodialysis (MHD) patients from the U.S. is still scarce and an association with race and ethnicity is unknown. We explore antibody dynamics in MHD patients from three U.S. states with a diverse racial and ethnic background.

Methods: We obtained consent from MHD patients with COVID-19, confirmed by RT-PCR, from 12 clinics. Phase 1 antibody testing was done between June and August 2020. Re-testing was done 6-8 months later. Antibodies were tested with an emergency use authorized assay (Diazyme DZ-LITE SARS-CoV-2 IgG CLIA kit). Linear mixed-effects models were employed to estimate the IgG half-life in patients with repeated IgG measurements. Patients were stratified by sex, race, ethnicity, obesity, and medians of age, dialysis vintage and body mass index.

Results: 104 patients (age 63.8±13 years, 67 (64.4%) males; 48 (46.2%) African-American, and 34 (32.7%) Hispanics) were studied. IgG was obtained 82 days (range 13 to 151) and 253 days (range 170 to 309) post-COVID-19. At initial testing, 101 (97.1%) patients were positive for IgG, 89 of them were available for repeated testing, where 74 (83.1%) showed persistent IgG. The luminescence signal was declined by 35.5 AU/mL (95% CI 28.7 to 42.4) from 47.8 ± 44.9 to 12.3 ± 21.1 AU/mL (P=0.0001; paired t-test, Figure 1). The estimated half-life of IgG was 62.8 days (95% CI 56.8 to 68.8). We observed no significant differences in the stratified analysis (Table 1; all p > 0.05).

Conclusions: The half-life of IgG against SARS-CoV-2 was approximately 63 days, corroborating reports from both the general and other MHD populations. Importantly, we found no association between IgG half-life, race and ethnicity.

PUB016

Incidence and Risk Factors for SARS-CoV-2 Infection in Patients with Lupus Nephritis

Background: Patients with lupus nephritis (LN) are known to be at higher risk for severe infections due to both an underlying immune dysfunction and as a consequence of immunosuppressive therapy (IS). We sought to investigate the impact of COVID-19 pandemic in patients with LN.

Methods: A total of 95 patients with LN actively monitored in our department between 26th February 2020, when the first case of COVID-19 was diagnosed in Romania, and 1st May 2021 were included in the study. Demographics, comorbidities, clinical and laboratory characteristics, current IS therapy, COVID-19 symptoms and outcome were collected. A COVID-19 diagnosis was made if clinical symptoms were accompanied by a positive SARS-CoV-2 PCR.

Results: Fifteen patients (15.8%) were diagnosed with COVID-19 at a median 279 days (IQR:218-341) since the first case was diagnosed in Romania. The majority of infections were mild (73.3%), moderate infections being encountered in the remaining patients (26.7%), while none has developed a severe infection. The most common
symptoms were fatigue (73.3% of patients), followed by loss of taste and/or smell (53.3%) and fever (46.7%). Overall, 40% of patients were hospitalized for a median of 11.5 days (IQR: 3.75-14). Of these, 2 patients needed supplemental oxygen and 1 patient non-invasive ventilation. There were no COVID-19-related deaths during the study period. Of the clinical variables associated with infection development, fewer patients with COVID-19 were on hydroxychloroquine (46.7% vs. 89%, p<0.04) or were on clinical remission during the study period (40% vs. 67.5%, p=0.04), while the median maintenance oral corticosteroid dose was significantly higher in those with SARS-CoV-2 infection compared to those without [16 mg (IQR: 7-21) vs. 6 mg (IQR: 4-10), p=0.007]. In multivariate Cox regression analysis, use of hydroxychloroquine (HR, 0.23; 95%CI, 0.04-1.26) and oral corticosteroid dose (HR, 1.11; 95%CI, 1.01-1.22) remained the most important predictors of COVID-19.

Conclusions: The burden of SARS-CoV-2 infection in patients with LN seems to be low. Use of hydroxychloroquine seems to be associated with a lower risk for COVID-19, while different immunosuppressive agents corticosteroid dose was identified as an independent risk factor for infection development.

PUB017
Long-Term Mortality Risk of Hemodialysis Patients Surviving Initial COVID-19: A Report from the Quebec Renal Network COVID-19 Study

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Background: Dialysis patients are at high-risk of morbidity and mortality early after SARS-CoV-2 infection. Long-term consequences of SARS-CoV-2 infection are however still not well described in this population. We aimed to compare long-term mortality between dialysis patients who survived 30-day after a SARS-CoV-2 infection and dialysis patients negative to SARS-CoV-2.

Methods: We included patients with SARS-CoV-2 PCR tests performed between March 1st 2020 and February 30th 2021 from 7 dialysis centers in Quebec. Patients alive 30 days after SARS-CoV-2 diagnosis were matched by age, sex, center and PCR test date to patients negative for SARS-CoV-2 and followed for up to one year, starting at 30 days after initial infection (or negative test). We assessed mortality risk in unadjusted and adjusted multivariable Cox regressions.

Results: Ninety-eight patients with SARS-CoV-2 infection alive 30-day after diagnosis were matched to 166 SARS-CoV-2-negative patients. Baseline characteristics were similar between the two groups. Patients were followed for a median of 331 (301-347) days. Overall, 32 patients died during the study period (15 [15%] in the SARS-CoV-2-positive group and 17 [10%] in the SARS-CoV-2-negative group, p=0.22). There was no statistically significant association between mortality risk and previous SARS-CoV-2 infection (HR 1.5, 95% CI 0.8-3.1), even after adjustment for residual imbalance (aHR 1.4, 95% CI 0.7-3.1). Results remained similar after exclusion of 4 patients who died of SARS-CoV-2 infection > 30-day after diagnosis (Table 1).

Conclusions: One-year survival of dialysis patients surviving SARS-CoV-2 infection was similar to those never infected.

Funding: Government Support - Non-U.S.

PUB018
Impact of COVID-19 on Hemodialysis Patients: The Quebec Renal Network (QRN) COVID-19 Study

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Background: Hemodialysis patients had to face numerous challenges during the COVID-19 pandemic. They are at increased risk of severe complications of COVID-19 and continued to visit hospitals three times weekly, increasing their risk of being infected. The objective of this study was to document the impact of the COVID-19 on patient’s experience in hemodialysis in Quebec.

Methods: Between November 2020 and May 2021, we conducted semi-structured interviews with 20 patients who were undergoing dialysis treatments in six hemodialysis units in Montreal. Interviews were transcribed and analyzed using thematic content analysis.

Results: Patients were satisfied by the measures implemented within their units in order to prevent COVID-19 outbreaks, such as making masks mandatory, restricting access to the dialysis ward, and even limiting the number of accompanying persons allowed. Participants reported that following the public health guidelines (social distancing, wearing a mask and washing hands) was easy and important in order to ensure their own and their family members’ safety. Because of this, participants were more likely to refuse to see their family resulting in feeling of isolation. This was particularly relevant for Indigenous patients who were having their hemodialysis treatment away from their home and family. This sub-group experienced particular issues due to the prolonged remoteness from their loved ones, change in their hemodialysis center and with the measures put in place by the hotel they were residing at. Even though their usual routine outside dialysis might have changed due to the pandemic, hemodialysis treatments allowed patients to keep a certain normality in their lives. Positive consequences were mentioned such as frequent contact through telemedicine and the existing solidarity between patients during the pandemic.

Conclusions: Patients undergoing hemodialysis faced particular challenges due to the COVID-19 pandemic. Nonetheless, they showed great resilience in their capacity to adapt to the new reality of their hemodialysis treatments.

Funding: Government Support - Non-U.S.

PUB019
Financial Hardships in a Population of Inner-City Dialysis Patients During the COVID-19 Pandemic and Relationship to Attitudes About Dialysis

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Background: We studied inner-City hemodialysis pts who reported financial difficulties and how this affected their attitudes towards dialysis and other aspects of life during the height of the COVID-19 pandemic.

Methods: 21 randomly selected hemodialysis pts were interviewed by telephone during the summer of 2020 using the Stress and Social Support Survey, the Attitude Towards Dialysis survey and questions regarding food scarcity, financial stressors, and feelings about COVID-19.

Results: There were 12 (57%) female, 9 (42%) male, 20 (95%) Black, 1 Other, mean age 53.7±4 yrs, mean yrs on dialysis 9.0±1.1, 3(15%) employed, 7 (35%) on disability, 55% (11) reported that finances affected how well they could control their medical condition (FIN+). FIN+ were more likely to agree that it was difficult to buy their medications because of expense (r=0.58, p=0.007), that they made dialysis a priority (r=0.5, p=0.03), could discuss their financial concerns with their MD (r=0.75, p<0.001), and that their healthcare team was a source of support (r=0.65, p=0.002). There was no difference in age, insurance type, education or gender but FIN+ pts had much lower mean BMI (21.1±1.1 vs 20.3±1.1, p=0.001) due to lower weight (67.6±7.3 vs 88.8±4.9 kg, p<0.001). No pt was receiving SNAP benefits and there was no difference in albumin or creatinine. FIN+ were more likely to believe they knew how to protect themselves from COVID (r=0.98, P<0.001), and did not fear COVID-19 itself, but were more likely to report feeling things were out of control during the preceding several weeks (r=0.9, p<0.05).

Conclusions: In our population of Inner-City Dialysis pts: 1. Over half of pts surveyed reported financial stress and were more likely to report difficult affording medication, but were more reliant on the dialysis team for social support and made dialysis a priority. 2. Pts reporting financial stress weighed significantly less, although mean creatinine and albumin values did not differ. 3. Pts living alone. 4. These patients were not afraid of COVID-19 and felt knowledgeable, but reported feeling out of control, possibly due to financial stressors affecting other aspects of their lives, including ability to pay for food.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
AKI-D in Ventilated Critical Patients with COVID-19

Background: Acute Kidney Injury (AKI) is a frequent complication in critical patients with Coronavirus Disease 2019 (COVID-19) and has been associated with a poor prognosis, especially when it is necessary to implement renal replacement therapy (KTR). The mortality reported in COVID-19 patients with AKI and KTR (AKI-D) is variable according to studies published today.

Methods: In this retrospective cohort study, we analyzed the clinical characteristics, comorbidity and prognosis of 87 COVID-19 patients, older than 18 years, ventilated and AKI-D between March 2020 and February 2021. We divided our patients into two groups: Group 1: Patients who start KTR in the period of time between the onset of COVID-19 symptoms and day 21. Group 2: Patients who initiate KTR after day 21 of the onset of COVID-19 symptoms. The Charlson Comorbidity Index and SOFA Score were calculated on the day of admission to hemodialysis.

Results: Our cohort of 87 patients had a mortality 95%, Group 1: 98%, Group 2: 82%. We found no significant differences in age, SOFA before KTR, Charlson score, AKI at admission and survival after the start of KTR between the two groups. Of the total patients, 10 recovered kidney function; four patients were discharged from hospital without KTR (1 from group 1 and 3 from group 2), the other six died during hospitalization. 29 patients (33,3%) died within 48 hours of starting dialysis, with a median pre-KTR SOFA: 15 (IQR =13-16).

Conclusions: In this study, a high mortality is reported, particularly in ventilated patients with the need for KTR in the first 21 days from the onset of COVID-19 symptoms (Group 1). We observed an excess of mortality compared to Group 2. We assume that it may be due to the severity of the underlying viral condition during the initial days of infection, a matter that would become less relevant as time goes by.

Cardiac Troponin and AKI in COVID-19 Sepsis-Related Patients
Beatriz V. Wofford, Marcelo R. Bacci. Faculdade de Medicina do ABC, Santo André, Brazil.

Background: The COVID-19 pandemic become the major reason of hospitalization of patients in ICU worldwide. AKI is a major disease and continue closely related with sepsis and COVID-19 infection. Cardiac injury is frequent in patients with septic shock and higher levels of cardiac troponin are expected in AKI patients however whether this is related with a poor outcome in the pandemic scenario still remain unknown. The objective of the study was evaluate the impact of the occurrence of AKI and cardiac troponin levels in patients with severe SARS-CoV-2 infection and their major outcomes

Methods: We conducted an observational study during COVID-19 pandemic in 2021 first wave outbreak in Brazil. The research was approved by the Ethics in Research Committee of the Hospital Israelita Albert Einstein. The sample included 86 hospitalization with COVID-19 of 18 years or older. The inclusion criteria were the occurrence of COVID-19 infection confirmed by oropharyngeal swab in the last 3 days of admission and the need of permanent of at least 3 days. Patients with a poorer expectancy of survival in the next 24 hours of inclusion were not considered eligible. Blood sample at admission was used to confirm sepsis and AKI and the patients were followed daily until discharge of the unit or death. AKI occurrence was seen as the rise of serum creatinine happened according KDIGO AKI guideline. Patients were divided in groups regarding the development of AKI and major outcome (mechanical ventilation or death).

Results: A total of 86 patients with sepsis were included. Female patients represented 58.3% of the patients. About 96,51% of the patients had at admission a level of d-dimer above 500 ng and 77.91% of patients had a cardiac troponin I above 20 ng in AKI patients group with a p level of 0.003. About 44 patients had AKI due to COVID-19 sepsis in the ICU, among those, 24 were already admitted in the ICU Median serum cardiac creatinine at admission was 2.44 mg/dL (1.64-4.02). There was a higher proportion of patients in mechanical ventilation with development of AKI after admission (14) than those without AKI during the whole hospitalization (11) with a p of 0.299. The mortality of patients with higher cardiac troponin were significantly higher in AKI patients than the non AKI patients.

Conclusions: In patients with COVID-19 sepsis related disease, there is a positive correlation between AKI and higher levels of cardiac troponin and higher days with mechanical ventilation.

COVID-19 and Kidney Disease: A Follow-Up Study
Marta De Filippo, Marco Simonini, Lorenza Citterio, Simone Fontana, Teresa Arcidiacono, Paolo Betti, Elena Cinel, Rebecca De Lorenzo, Paolo Manunta, Patrizia Rovere Querini, Chiara Lanzani. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: It is well known that SARS-CoV-2 infection is associated with the development of acute kidney disease; however, not much is known about the long-term kidney effects of this pathology.

Methods: We analyzed kidney function data during hospitalization and subsequent follow-up (6 months) of 150 (of which 51 with CKD) patients hospitalized for COVID-19.

Results: 28% of subjects developed AKI during hospitalization; proteinuria and microhematuria were present in 53% and 43% respectively (p<0.01), whereas with the 2nd there was a lower albumin and PTH (p=0.01) and an association with female sex (p=0.02) and sex (p=0.01). Similarly, WR also showed higher cCI and lower PTH after the 1st (p=0.02) and 2nd doses (p=0.01), adding older age (p=0.03) and lower albumin (p=0.05) to the 2nd. After both inoculations, WR subgroup was associated with age over 75 yo (p=0.03); female sex (p=0.01), CCI over 8 (p=0.01), CVC over AVF/AVG (p=0.01), dialysis vintage under 24 mo (p=0.01) and PTH under 150 μg/L (p=0.01). A model combining CCI, sex (male) and vascular access (CVC) as a regression model associated those factors to WR after the 2nd dose with OR (95% CI): 1.81 (1.06-3.08); 0.05 (0.01-0.65); 13.55 (1.06-174.18), respectively (p=0.01).

Conclusions: Older age, high CCI, low PTH and albumin, CVC over AVF/AVG and recently started dialysis (less than 2 years) relate to lower response. High comorbidity burden is suggested as a more significant risk factor than age alone. The role of PTH as a marker of low immunogenicity in the HD population should be target of further investigation. Signalization of HD patients at risk of low response may play a key role in policy making, namely the necessity for booster doses, follow-up measurements and isolation methods.
COVID-19 and Kidney Transplantation in a Colombian population
Carlos E. Duran, Mayra A. Estacio, Daniela Espinosa, Fredy S. Lozano, Juan Posada, Liliana Mesa, Johanna Schweinberg. Fundacion Valle del Lili, Cali, Colombia.

Background: Patients with kidney transplants seem to be at particularly high risk for severe COVID19 disease due to their impaired immune responses and comorbidities

Methods: We performed an observational study of kidney transplant recipients with SARS-CoV2 infection admitted at Fundación Valle del Lili from June to December 2020. To be eligible for this study, patients have symptoms compatible, a positive RT-PCR and inpatient management. Asymptomatic patients were excluded

Results: We enrolled a total of 50 patients. 64% were male, and the median age was 53.5 years (range 46-60). The comorbidities were: 36(70%) hypertension, 16(32%) diabetes mellitus, 5(10%) obesity. The most common immunosuppressive regimen was tacrolimus 76% and prednisone 88%. The median time from symptoms onset to the positive RT-PCR was 7 days. The most common initial symptom was fever (64%), and fatigue (44%) and dyspnea (36%). Baseline levels of CRP was 6.43 mg/dL (3.25-11.22). The median lymphocyte count was 785 mm3/uL (550-1230). Baseline D-Dimer was 0.767 ug/ml (0.484-1153.5), ferritin median level was 1011ng/ml (670-2145). Clinical outcomes are shown in Table. Six of the patients died (12%), 4/6 were by sepsis-related multi-organ failure and 2/6 were by ARDS

Conclusions: Major complications such as acute kidney injury, acute respiratory distress syndrome and mortality related to COVID-19 infection observed in our study are lower than those reported in other countries

Clinical outcomes of the hospitalized patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No (%)</th>
<th>Yes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>27.9%</td>
<td>72.1%</td>
</tr>
<tr>
<td>ICU stay</td>
<td>13.3%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>13.3%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>11.1%</td>
<td>88.9%</td>
</tr>
<tr>
<td>Days of NOV isolation</td>
<td>11-31.7</td>
<td></td>
</tr>
<tr>
<td>Hospital stay</td>
<td>11-110.6</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>20-100</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Hemodialysis</td>
<td>3-18</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>3-18</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1-22</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
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<tr>
<td>Vasopressor</td>
<td>19-31</td>
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<tr>
<td>Anticoagulant</td>
<td>1-22</td>
<td></td>
</tr>
</tbody>
</table>

PUB025

Predictors of In-Hospital Mortality Among Hospitalized Patients with COVID-19 and AKI: A Single-Center Study
Bennett W. Wisner,1 Sahitya Allam,2 Abhijit Ravindran,1 Kambiz Kalantari.3 1University of Virginia School of Medicine, Charlottesville, VA; 2University of Maryland Medical System, Baltimore, MD; 3University of Virginia, Charlottesville, VA.

Background: AKI and COVID-19 infection are both independently associated with high mortality rates and those with COVID-19 who develop AKI have higher mortality rates. We investigated the predictors of mortality in patients admitted to our hospital with COVID-19 who developed AKI during their hospital stay.

Methods: We conducted a retrospective analysis of all patients hospitalized at University of Virginia Medical Center for COVID-19 infection who developed AKI from March 2020 through April 2021. In-hospital mortality was defined as death during admission or within 7 days of discharge to hospice. Data on patients’ demographics, comorbidities, AKI stage, dialysis requirement, admission to ICU, serum albumin, ferritin, d-dimer, fibrinogen, hemoglobin, as well as mortality at hospital discharge and 90 days were collected through chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with in-hospital mortality.

Results: 219 patients qualified for study inclusion criteria. The average age was 62.2 years and 56.6% of patients were men. The in-hospital mortality rate was 27.9%. An additional 1.37% died in the 90-day follow-up period. Age (p = 0.049), AKI-D (p < 0.001), AKI stage (p = 0.001), serum albumin (p < 0.001), and ICU admission (p < 0.001) were associated with mortality in the univariate analysis (Table 1). After adjustments for covariates, age (p < 0.001), AKI-D (p < 0.001), and ICU admission (p < 0.001) were predictors of mortality in our multivariate analysis [AUC: 0.863, 95% CI (0.815-0.911)].

Conclusions: Age, dialysis requirement, severity of AKI, and ICU admission are predictors of mortality among patients with COVID-19 and AKI at our institution.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Impact of COVID-19 in Quebec Hemodialysis Units: Health Care Providers’ Experiences

Mary-Chantal Fortin,1,2 Aliya O. Afzal,3 Marie-Francoise A. Malo,2 Fabian A. Ballesteros Gallego,1 Annie-Claire Nadeau-Fredette,2 William Beaubien-Souligny,3 Rita Suri,1 Centre Hospitalier de l’Universite de Montreal Centre de Recherche, Montreal, QC, Canada; 3McGill University Faculty of Medicine and Health Sciences, Montreal, QC, Canada.

**Background:** Chronic kidney disease is a risk factor for the severe form of COVID-19 and the hemodialysis unit represents a high-risk setting for virus transmission. Healthcare providers (HCPs) have the duty to keep patients safe and healthy, and also to protect themselves from the virus. The objective of this study was to gather health care provider experiences regarding COVID-19 infection and dialysis units.

**Methods:** We conducted semi-directed interviews by phone or video with 21 HCPs working in 6 hemodialysis units - nurses, nephrologists, pharmacists, social workers, security agent and housekeeping attendant - between November 2020 and May 2021. The content of the interviews was analyzed using thematic content analysis.

**Results:** Participants identified positive and negative impact of COVID-19 pandemic. In their professional life, HCPs declared developing more collaboration, creativity and mutual support. However, due to the pandemic restrictive measures and lack of resources, HCPs felt a lot of distress not being able to provide adequate care for patients’ needs. Participants also reported disruption in communication between HCPs and patients because of physical distancing and wearing a mask. They also described problems associated with patient transportation leading to delays or even absence of patients to their treatment. In their personal life, some HCPs declared being concerned by these new challenges at work and reported difficulties balancing work and family life. Also, most of them feared to contaminate their family and adopted certain routine cleaning to alleviate this fear.

**Conclusions:** HCPs working in hemodialysis unit faced multiple challenges during the COVID-19 pandemic that impacted their wellbeing. However, they have shown high level of resilience and dedication to ensure health care delivery and to support hemodialysis patients.

Funding: Government Support - Non-U.S.

Renal Manifestations and Their Association with Mortality in COVID-19 Patients at a Safety-Net Hospital

Sandra Gomez Paz,1 Eric Lam,2 Luis González Mosquera,3 Diana Cardenas-Acosta,1,2 Joshua Fogel,1,2 Sofia Rubinstein.1

**Background:** Renal involvement in COVID-19 leads to severe disease and higher mortality. We study additional previously not studied renal parameters in COVID-19 patients and their association with mortality.

**Methods:** A retrospective study (n=340) of confirmed COVID-19 patients with renal involvement determined by the presence of acute kidney injury. Multivariable analyses of logistic regression for mortality and linear regression for length of stay (LOS) were adjusted for relevant demographic, comorbidity, disease severity, and treatment covariates.

**Results:** Mortality was 54.4% and mean LOS was 12.9 days. For mortality, creatinine peak (OR:35.27, 95% CI:2.81, 442.06, p<0.01) and persistent renal involvement at discharge (OR:4.47, 95% CI:1.99,10.06, p<0.001) were each significantly associated with increased odds for mortality. Increased blood urea nitrogen peak (OR:0.98, 95%CI:0.97,0.996, p<0.05) was significantly associated with decreased odds for mortality. For LOS, increased blood urea nitrogen peak (B0.001, SE<0.001, p<0.01), renal replacement therapy (B0.19, SE:0.06, p<0.01), and increased days to acute kidney injury (B0.19, SE:0.05, p<0.001) were each significantly associated with increased length of stay.

**Conclusions:** As persistent renal involvement at discharge is associated with increased odds for mortality, this suggests that early identification of renal involvement characteristics in COVID-19 patients is useful for treatment management. Clinicians should focus on renal parameters of blood urea nitrogen peak, renal replacement therapy, and days to acute kidney injury for predicting patient length of stay.

Renal and Cardiovascular Events Following Moderna SARS-CoV-2 Vaccination

Maryam Sattari, Jourdan A. McKinnis, Amir Kazory. University of Florida College of Medicine, Gainesville, FL.

**Introduction:** While knowledge about coronavirus disease of 2019 (COVID-19) has been rapidly growing, healthcare systems are still challenged by uncertainties surrounding currently available preventive measures. The mRNA-1273 vaccine (Moderna Inc., Cambridge, Massachussets, USA) encodes the spike glycoprotein of the coronavirus. Whereas at the site of injection and headache are among the most recognized adverse events, little is known about the vaccine’s less frequent side effects in the setting of rapid deployment.

**Case Description:** 1 A 71-year-old man noted frank blood in his urine the day after he received his second dose of Moderna COVID-19 vaccine. He also experienced two episodes of epistaxis. The patient’s past medical history was significant for a non-ST elevation myocardial infarction about 2 months prior to presentation, after which he had been on aspirin 81 mg daily and clopidogrel 75 mg daily. Lab results were significant for normochromic normocytic anemia. Both hematuria and epistaxis resolved without intervention, and he has not had any further bleeding episodes to date. 2 A 72-year-old man noted “wine-colored” urine the day after he received his second dose of Moderna COVID-19 vaccination. His past medical history was significant for a remote history of nephrolithiasis (22 years ago and a stone in his right kidney). He recently developed increased proximal microhematuria and rhabdovirus 20 mg daily. Urine dipstick confirmed large blood. Hematuria resolved completely after cystoscopy with bladder irrigation and has not recurred to-date.

**Discussion:** COVID-19 Moderna post-vaccination bleeding events (e.g. epistaxis or retroperitoneal bleeding) have been reported as infrequent adverse events. While actual COVID-19 vaccine infection has been rare in those with hematuria or epistaxis with Moderna vaccine following the second dose of the Moderna vaccine has also been reported in patients with IgA nephropathy. However, to our knowledge, these are the first two reported cases of gross hematuria associated with Moderna COVID-19 vaccine in mainstream health literature without history of kidney disease. Raising the awareness of clinicians is important in that entering these events into the vaccine adverse events reporting system can clarify their true incidence. Whether these patients need to be followed to determine if they will develop signs of a previously undiagnosed nephrolithic disease in the future remains to be elucidated.

Vitamin D Levels and COVID-19 Outcome Among ESKD Patients in a Urban US Hemodialysis Population

Derrick E. Ridley,1 Anjana Easwar,1 Omar Syed,2 Marcellus Edwards,3 Spencer A. King,3 Rosie Jardina,1 Jose E. Navarrete,1 Harold A. Franch,1 Janice P. Lea,1 Jason Cobb.1 Emory University School of Medicine, Atlanta, GA; 2Morehouse School of Medicine, Atlanta, GA; 3New York Institute of Technology, Old Westbury, NY, *Emory Healthcare, Atlanta, GA.

**Background:** Due to logistical constraints of in-center hemodialysis (HD) ESKD patients, we endeavored increased risk during the COVID-19 pandemic. Minorities are overrepresented in ESKD, making this group more susceptible to poor outcomes given existing racial disparities. Studies have emerged spotlighting vitamin D’s effects on autoimmune regulation of immune function and the relevance of extra-renal one alpha hydroxylase. Many studies describe links between vitamin D deficiency and severity of SARS-CoV-2 infection in high-risk patients, but there is a paucity of data specific to ESKD patients. This study explored the association between vitamin D status and COVID-19 infection in a primarily black HD population.

**Methods:** Emory Dialysis patients’ vitamin D levels [25(OH) D] were collected November 2020 as part of a quality improvement project. All SARS-CoV-2 positive HD patients were identified (October 2020 to April 2021). Retrospective chart review including baseline data and labs were collected. An unpaired t-test was used to compare vitamin D levels between COVID-19 positive and negative patients.

**Results:** 620 patients were included. All patients enrolled in-center HD three times per week. Patient identified race makeup included black (n=570) and non-black n= 50. Average age was 59 years. Gender: males (n=324) and females (n=296). 73 patients died in 2019 COVID-19 and 68 patients identified as black race. Average vitamin D levels for COVID-19 positive patients 27.33 and COVID-19 negative patients 26.2 (p=0.55).
Average PTH in COVID-19 positive patients 507.3±371 and COVID-19 negative patients 557.8±72.4. Calcium level in COVID-19 positive patients 8.7±4.66 and COVID-19 negative patients 8.73±0.72 (p=0.48). Relative risk of developing COVID-19 in black HD patients was 1.14 compared to others (p=0.75).

Conclusions: Our study showed no statistically significant correlation between Vitamin D level and COVID-19 acquired AKI. The role of vitamin D deficiency as a risk factor and the role of Vitamin D supplementation for prevention or treatment COVID-19 in this population is unclear. Further studies investigating the relation between Vitamin D levels and severity of COVID-19 infection in this population should be explored.

PUB031
Antibody Response Following Vaccination to SARS-CoV-2 in Dialysis-Dependent Patients
Lauren Floyd, Chad L. Pardoe, Ajay P. Dhaygude. Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom.

Background: SARS-CoV-2 is a novel virus resulting in the loss of lives globally. Recently it is recognised that dialysis dependence and end stage renal disease are risk factors for severe COVID-19 infection. In addition, those receiving renal replacement therapy are thought to be immunosuppressed as a result of persistent uraemia and chronic inflammation. The effects of immune dysfunction including T and B cell suppression have caused concerns that haemodialysis (HD) patients may have a reduced immunological response to the vaccine. Recent studies looking at SARS-CoV-2 antibodies demonstrated different outcomes, with some showing diminished antibody responses following vaccination in HD patients whilst others suggest good efficacy and persistence of antibodies.

Methods: In January 2021 Royal Preston Hospital, UK, commenced a COVID-19 vaccination programme for all HD patients in accordance with the UK government advice and guidelines. In May 2021 a prospective study included 546 patients receiving in centre and home HD started. SARS-CoV-2 antibodies are being collected during routine dialysis visits and serum samples for spike and nucleocapsid proteins are being measured as markers of immune response. Antibodies are measured monthly alongside secondary outcomes including hospital admissions, mortality and subsequent COVID-19 infection. This study has been approved by the Health Research Authority and the Research and Development team at Lancashire Teaching Hospitals NHS Foundation Trust.

Results: Data collection is ongoing. Sixteen patients (2.9%) declined the vaccine and the majority (85.1%) received the Oxford-AstraZeneca vaccine. The median age is 63.34 years (IQR 54-75 years) and there is a 59.9% male predominance (n=327). 48 patients (10.5%) are receiving home haemodialysis and the remaining 498 patients receive in centre haemodialysis on a twice or thrice weekly basis. Initial results are due in June 2021 and 6 month data will be available in November 2021.

Conclusions: We aim to quantify antibody response to the COVID-19 vaccine in HD patients. This will potentially allow us to identify those patients who may still be at risk of COVID-19 despite vaccination and guide further management options in the future. Ongoing research and data analysis is required to investigate both the initial and chronic immune mediated response.

PUB032
Mortality Among ESKD Patients with COVID-19: Comparison Between Kidney Transplant and Hemodialysis
Muhammad Abdulbasit, Omar Salameh, Mujahed M. Dauleh, Ali M. Zebi, Navin Verma, Nasrollah Ghahramani. Penn State College of Medicine, Hershey, PA.

Background: The COVID-19 pandemic has had an impact almost on every aspect of human life. With more than 170 million cases and more than 3.5 million deaths worldwide (as of May 30, 2021), new facets of the fallout are being uncovered day after day. We analyzed the effects of COVID-19 on end stage kidney disease (ESKD) patients and compared the demographic profile and mortality in patients on hemodialysis (HD) to those who received kidney transplant (KT) in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated electronic medical records network, to identify 3601 ESKD patients ≥18 years who had either received a kidney transplant (KT) (n=1849 from 31 HCOs) or had been on dialysis before 12/31/2019 (n=1752 from 31 HCOs) and who had been diagnosed with COVID-19 infection between 1/1/2020-12/31/2020. We used the KT group as the reference and calculated the comparative risk of 6-month mortality after COVID-19 infection between 1/1/2020-12/31/2020. We used a prospective multi-center cohort, prior to offering 2nd doses.

Results: Of all the variables collected, only age was associated with mortality. Using Cox regression analysis no treatments were associated with survival, including thrombolytic administration, full dose anticoagulation, IL-6 administration, plasma, and hydroxychloroquine. Of all the variables collected, only age was associated with mortality.

Conclusions: Acute kidney injury requiring renal replacement therapy carried significant mortality in the early stages of the pandemic. Our numbers are similar to, but less than the other reports from New York area hospital systems which had a mortality rate of 79%[3]. Our initial numbers may be partially explained by the population served by the New York City public hospital system. As our experience with this disease expands, hopefully our management of AKI in these patients will improve.

PUB033
Outcomes in Critically Ill COVID-19 Patients with AKI Requiring Renal Replacement Therapy
Aaron Douen, Gregory M. McGrav, Bei Xiong, Rohan Banan, Samantha J. Allen, Elena Frolova, Adel S. El-Hennawy, Winston Lee. ‘New York City Health and Hospitals Coney Island, Brooklyn, NY; ’St.George’s University, School of Medicine, True Blue, Grenada.

Background: In the past year acute kidney injury(AKI) has been shown to be a cornerstone complication of critical illness associated with COVID-19[1], with 60%-70% of all patients in ICU developing AKI and needing renal replacement therapy (RRT) [2]. There are still many facets of the novel corona virus’ effect on the kidneys and our approach has changed over time. We report on our experience with AKI requiring RRT early on in the pandemic.

Methods: We performed a retrospective chart review between the month of April to July 2020 at Coney Island Hospital, a public hospital in New York City. Upon identifying those with COVID-19 and AKI requiring RRT, we collected data regarding medications administered, inflammatory markers, demographic data and outcomes.

Results: 62 patients had AKI requiring RRT. 22.6% were female, 77.4% were males with the mean eGFR on admission being 57.54 ± SD of 29.4. Average age of our cohort was 63 years old. In our cohort the average max values of the following were: ferritin 3495, IL-6 284 and D-dimer 12,460. Average BMI of our cohort was 31 with SD of 7 (table 1). On average there was 16.5 days between initiation of dialysis and death. After initiation of RRT 30 day mortality and 90 day mortality was found to be 80.6% (50/62) and 87.1% (54/62) respectively. Overall 98.4% of the cohort died. Using Cox regression analysis no treatments were associated with survival, including thrombolytic administration, full dose anticoagulation, IL-6 administration, plasma, and hydroxychloroquine. Of all the variables collected, only age was associated with mortality.

Conclusions: Mortality rates from COVID-19 are significantly higher in patients requiring renal replacement therapy (20-30%) than the overall estimated mortality of 1-4% worldwide. COVID-19 vaccines offer a strategy to protect this vulnerable cohort. Patients on hemodialysis are at higher risk of exposure to COVID-19 due to an inability to self-isolate, and were prioritised for vaccination in the UK. The Oxford Astra-Zeneca (Ox/AZ) vaccine allows administration on the dialysis unit, due to ease of storage and transportation. During the time period between the 1st and 2nd dose in the vaccination schedule, a rare clinical syndrome of thrombocytopenia and thrombosis was observed in patients after receiving the Ox/AZ vaccine.

Methods: We undertook a retrospective analysis of routine dialysis bloods, examining any significant changes in platelet count pre and post vaccine in our dialysis cohort, prior to offering 2nd doses.

Results: Data for 780 hemodialysis patients with platelet count pre and post first dose COVID-19 vaccine were analysed. Of these, 471 patients received the Ox/AZ vaccine, 145 received Pfizer, and the remainder were vaccinated elsewhere, therefore data on vaccine type not available. Mean platelet count for the whole cohort before vaccination was 215±10 L, and post was 218±10 L. 126 patients had a platelet count below 150±10 L pre-vaccine, and this number was the same post vaccination. No difference was observed based on vaccine type (see table).

Conclusions: No signal of vaccine-induced thrombocytopenia was detected in this cohort, though the numbers were small to detect such a rare event. The benefits of completing the vaccine schedule outweigh any small risk of vaccine-associated thrombocytopenia and thrombosis in this clinically extremely vulnerable cohort.

Results of platelet count changes pre post COVID-19 vaccination by Vaccine type

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Platelet count pre vaccine</th>
<th>Platelet count post vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ox/AZ</td>
<td>215±10 L</td>
<td>218±10 L</td>
</tr>
<tr>
<td>Pfizer</td>
<td>215±10 L</td>
<td>218±10 L</td>
</tr>
</tbody>
</table>

Platelet count values given as 10^11/L.
The Tale of Two Collapsing Glomerulopathies Associated with COVID-19 in Stamford Hospital
Mariana A. Chang, Revekka Babayev. Stamford Hospital, Stamford, CT.

**Introduction:** One pattern of kidney injury seen in COVID 19 is collapsing glomerulopathy (CG), a type of Focal Segmental Glomerulosclerosis (FSGS). It has been hypothesized that direct viral effect or increased circulating cytokines from the inflammatory response of the virus, or both, can lead to CG especially in patients with high-risk alleles of APOL1 gene.

**Case Description:** Patient 1: 63-year-old man, COVID-19 positive, who received only supportive care while hospitalized (Results in table 1). Patient 2: 62-year-old man, COVID-19 positive, who required brief treatment with dialysis and received high-dose steroids (Results in table 1).

**Discussion:** We present 2 cases who achieved partial renal recovery despite different treatments, raising the question of the role of steroids in patients with COVID-associated CG.

Table 1

<table>
<thead>
<tr>
<th>Renal biopsy (Patient 1) showing glomerular collapse</th>
</tr>
</thead>
</table>

Impact of First vs. Second COVID-19 Surge in Dialysis Patients in San Antonio
Mohammad Sadeddin, Thuylinh M. Nguyen, Nicholas S. Niazi, Shweta Bansal. The University of Texas Health Science Center at San Antonio, San Antonio, TX.

**Background:** San Antonio, Texas witnessed a COVID-19 surge during July and December 2020. COVID-19 had disproportionately severe impact on dialysis population during first surge; however, experiences from second surge is not known. The aim of our study is to compare the effect of two surges on prevalence and outcomes of COVID-19 infections in dialysis patients within University Health System.

**Methods:** First surge was from April 20 to Sept 20; second was from Oct 20 to Mar 21. Over12-month period, we recorded COVID-19 infections and outcomes for adult patients receiving dialysis at three centers (1st surge n=359 including 25 home and 2nd surge n=362 including 37 home). Demographic, clinical, laboratory, treatment and outcomes data were analyzed.

**Results:** COVID-19 infection were similar during surges (36 [10%] vs.43 [12%]). There was no difference in age, sex, ethnicity, smoking, co-morbidities, cause of ESKD, access and medications. However, patients during second surge were more obese (28 ±4.5 vs 30.4±7.5 kg/m² p=0.015), less dialysis vintage (6.2±4.5 vs. 5.7±3.1 yr, p=0.006), higher WBC (6.5±2.2 vs. 7.3±3.6 x 10³/ml, p=0.016), ferritin (939±719 vs. 1227±1621 µg/L, p=0.048), and D-dimer (2285±2120 vs. 5670±12410 IU ng/ml, p=0.02). No infection occurred in home dialysis patients during first surge compared to 6 (14%) during second surge (p=0.02). Table shows outcomes

**Conclusions:** Incidence of COVID-19 infections in our dialysis population were similar in the two surges. Hospitalization rates were similar, but more patients required ICU admission, ventilation and longer stay during second surge, although non-significantly. Death was significantly higher during second surge. Home dialysis patients more frequently affected than first surge suggesting change in health behaviors.

Table 1

<table>
<thead>
<tr>
<th>Renal biopsy (Patient 1 &amp; 2): Tubular microcyst formation; also seen in HIV-associated nephroptahy</th>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1st Surge (N=359)</th>
<th>2nd Surge (N=362)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization (%)</td>
<td>20 (56)</td>
<td>11 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Missing Information</td>
<td>4 (20)</td>
<td>2 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>N for Hospitalized Data</td>
<td>16</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>ICU (%)</td>
<td>5 (15)</td>
<td>3 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Ventilation (%)</td>
<td>1 (3)</td>
<td>3 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vasoconstrictor</td>
<td>2 (12.5)</td>
<td>2 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>8 (7-21)</td>
<td>10 (6-17)</td>
<td>NS</td>
</tr>
<tr>
<td>Dosing Time (h)</td>
<td>6 (5)</td>
<td>7.5 (5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Death (%)</td>
<td>1 (1)</td>
<td>7 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term mortality (%)</td>
<td>5 (5)</td>
<td>11 (2)</td>
<td>NS</td>
</tr>
</tbody>
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A Single-Center Experience: SARS-CoV-2 in ESKD and Kidney Transplant Patients

Angela Pauline P. Calimag,1,2 Dana Mueller,1,2 Anthony Guglielmi,1,2
Spencer Deleaevuex,2, Caroline Yousef,2, Vinay Raju,1,2 Edgar V. Lerman,1,2
1 Advocate Christ Medical Center, Oak Lawn, IL; 2 University of Illinois at Chicago, Chicago, IL.

**Background:** A new strain of coronavirus was first recognized in late 2019 resulting in a worldwide pandemic by early 2020. This pandemic challenged health care systems worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a spectrum of illnesses ranging from asymptomatic, mild, and self-limiting to severe disease. To this date, there are no clear treatment guidelines or protocols for the management of patients in general and for hemodialysis and transplant patients in particular. The Centers for Disease Control and Prevention (CDC) lists patients with chronic kidney disease and immunocompromised patients as high risk for severe disease from SARS-CoV-2.

**Methods:** Our study is a single-center retrospective study. We conducted an observational, retrospective study in ESKD and kidney transplant recipients hospitalized and diagnosed with COVID-19 disease at Advocate Christ Medical Center admitted between March 1 to May 31, 2020, a 3-month period. We describe our experience in patients with ESKD and kidney transplants during the COVID 19 pandemic. With particular attention to the treatments used, prognosis, and kidney outcomes in these patients.

**Results:** From the aggregate total of patients diagnosed with SARS-CoV-2 between March 1 to May 31, 2020, there were 34 patients with ESKD on KRT and 3 kidney transplant patients. The median age of our ESKD cohort was 63.5 years while the KT cohort was 69 years. For both patient populations were predominantly male with 52.9% for ESKD and 66.7% for KT. With 64.7% of ESKD being composed of African Americans, while our KT patients were predominantly Caucasian at 66.7%. The average length of hospital stay was longer for KT patients at an average of 22 days. The incidence of in-hospital death was significantly higher in ESKD patients at 27.8% while we had no mortality for KT pts. For in-patient mortality serum Na, K and BUN were not statistically significant from those who survived. D-dimer peak was significantly higher in mortality.

**Conclusions:** COVID-19 infection is associated with a high rate of mortality in ESKD patients with SARS-CoV-2. Monitoring D-Dimer levels may serve as a warning for development of AKI. Therefore, early intervention is still lacking as to the causal mechanisms and whether D-dimer levels can be used as a prognostic marker for in-hospital mortality. Tracking these markers may allow prediction of disease progression. Data on role of D-Dimer levels in AKI are scant.

**Hyponatremia appears to be protective for mortality and AKI in hospitalized COVID-19 patients.** Association of delta serum sodium (ΔSNa) defined by ΔSNa was associated 2% decrease the odds of developing AKI. Every one percent increase in ΔSNa were -4.6 mmol/L and 0.3 mg/dL from the baseline SCr 3-month prior, death, and length of stay (LOS) is examined by multiple logistic and linear regression as appropriate.

**Results:** Of 125 KT recipients, mean age±SD was 47.0±15.1 years old and 53% were male. The majority were White 87 patients (70%) followed by others 27 (22%), Asian 9 (7%), and Black 2 (1%) patients. Mean δNa was 133±6 mmol/L and δSNa were -4±5 mmol/L. Mean δASNa were -3.02±4.09%. Seven patients (6%) died, and 24 (19%) patients developed AKI. Every one percent increase in δASNa was associated 0.33 day increase in the LOS (95% CI: 0.03, 0.547, 95% CI: -7.6, 1.41). After adjusted by age, gender, race, presence or absence of diabetes or hypertension, the magnitude and direction of the association were similar in those all three outcomes.

**Conclusions:** Hyponatremia appears to be protective for mortality and AKI in KT recipients during COVID-19. Association of delta serum sodium (δASNa) defined by percent drop of admission serum Na (SNa) from a 3-month pre-admission SNa with outcomes including acute kidney injury (AKI) defined by rising serum creatinine (SCr) 0.3 mg/dL from the baseline Scr 3-month prior, death, and length of stay (LOS) is examined by multiple logistic and linear regression as appropriate.

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The Relevance of Urinalysis in the Hospitalization of Patients with COVID-19 and Nephrology Early Intervention
Lilia M. Rizo Topete,1,2 Giovanna Y. Arteaga Muller,1 Elisa M. Guerrero Gonzalez,1 Adrian Camacho-Ortiz,1 Luis C. Mata,1 Luis F. Rangel,1 Gabriela E. Aguilar Díaz.1 Hospital Universitario de Monterrey “José Eleuterio Gonzalez”, UANL; Hospital Universitario “José Eleuterio Gonzalez”, UANL, Monterrey, Mexico; 3Hospital Christus Manguera Alta Especialidad, Monterrey, Mexico.

Background: Multidisciplinary management of the COVID’s patients is essential for their evolution, and the early detection of AKI is a important role to avoid morbi-mortality. In March 2020, the pandemic by COVID-19 appeared in Mexico, and it led all the health system to change the intrahospital management.

Methods: In a retrospective, observational analysis of all the patients >18 Y that were hospitalized at the Hospital Universitario de Monterrey, in the COVID area, from March to August 2020, we notice how the urinary sedimentation evaluation from the beginning could detect patients who could develop AKI or the need of RRT. All data were analyzed using SPSS statistical software (version 25; IBM Corporation, Armonk, New York).

Results: A total of 344 patients hospitalized from March to August 2020. 220 patients with EGO since the beginning (obtained when our nephrology team take place on the presentational participation on AEMA) 102 did not have proteinuria, and, on the other hand, the rest (61 or 37%) reported it. 95 patients (41.7%) had hematuria. Hematuria were more likely to be treated with KRT. Patients with hematuria demonstrated an increased tendency to require RRT: 38.2% of patients with hematuria versus 11.6% without hematuria, the greater chance that needs RRT (P<.001).

Conclusions: The presence of active sedimentary urine on COVID patients is frequent. The patients who present the combination of hematuria and proteinuria develop severe AKI (KDIGO 3 without RRT) or the need for RRT. Factors in patients such as to be on their upper edge of 40 years old, the presence of hyperkalemia, metabolic acidosis, also the hematuria and proteinuria, suggest the AKI risk that required RRT.

PUB041
Thrombotic Microangiopathy Following COVID-19 Infection
Gabriela Gonzalez,1 Adrian Arteaga Muller,1

Background: Thrombotic Microangiopathy is a rare but significant complication of COVID-19 infection. Initial reports indicated that splenic and renal infarcts concerning primary antiphospholipid syndrome were further supported by positive serological testing confirming the presence of positive Antineutrophil antibody, Cardiolipin antibody, B2glycoprotein, and Lupus anticoagulant. In addition, the urinalysis showed active urinary sediment with dierospermic BSCs and nephritic range proteins. This patient had a kidney biopsy which was consistent with chronic TMA and was initiated on anticoagulation therapy with warfarin for antiphospholipid antibody syndrome.

Discussion: The possibility of occurrence of TMA following COVID-19 infection and the possible association between markers of endothelial activation, intravascular hemolysis, coagulation and organ damage in infection should be considered. This understanding is clinically relevant as it may necessitate the need for early APS antibody and TMA panel testing and initiation of anticoagulation in the amplified hypercoagulable state in COVID-19, especially in preventing life-threatening thrombosis.

PUB043
Algorithm for Predicting AKI
Shivangi Patel. Morristown Medical Center, Morristown, NJ

Background: Current detection of AKI relies on acute rise in serum creatinine (sCr) and/or a decline in urine output over given time interval. However, biomarkers for AKI have been shown to be elevated prior to change in sCr, suggesting that the time to intervene and prevent AKI is before the change in sCr occurs, when irreversible damage has already occurred. The purpose of the present study was to identify variables that would predict patients at risk for developing AKI without relying on sCr or urine output.

Methods: Retrospective chart review was conducted on all patients admitted from Jan. 1 to Jul. 31 of 2019. Cases were included if those that developed AKI defined as change in sCr >1.5mg/dL and those that did not develop AKI, a change of sCr <0.3mg/dL. After exclusion criteria, the final data set consisted of a total of 547 patients and was basis to detect variables that are readily available.

Results: Data showed that the higher the rise in sCr the worse the renal injury requiring renal replacement therapy and worse the patient outcome. sCr ≥ 1.5 x baseline correlated with prerenal or mild AKI, while contrast induced nephropathy correlated with ≥ 2x baseline sCr and acute tubular injury and need for renal replacement therapy correlated with ≥ 3x baseline sCr. 20 specific variables were identified in differentiating those that will develop AKI and those that did not develop AKI. Individually some variables weighed more than others in differentiating between AKI and no AKI, however same variables were present across any severity of AKI. Using the 20 variables a specific algorithm was developed to identify any patient admitted and their risk to develop AKI in any inpatient clinical setting. To confirm the accuracy of the data, the same variables were extracted via computer (instead of manually) on a new pool of 769 patients with retrospective admissions yielding same result as the clinician with 81% sensitivity, 80% specificity and 80% accuracy in detecting AKI.

Conclusions: The variables are readily available without need to change patient management or increasing cost. Further study is being conducted to answer the following: How early and accurately will this algorithm predict AKI? Will this prevent AKI by altering management of clinicians when alerted? This could potentially be integrated into hospitals’ electronic health records for real time patient monitoring and detection of early AKI and modify patient care and outcomes.

PUB044
Not Everything Is About COVID-19: An Unusual Case of Rhabdomyolysis and AKI After Physical Activity
Marcelio M. Dourado, Luiz H. Miranda. Multirim Universidade Federal de Pernambuco, Recife, Brazil.

Introduction: Rhabdomyolysis is the breakdown of striated muscle, leading to systemic manifestations that typically include myoglobinuria, being responsible for 5 to 7% of non-traumatic acute kidney injury(AKI). It can be caused by trauma, status epilepticus, metabolic myopathies, drugs, infections, thyroid disease and hemoglobinopathies.

Case Description: We report a case of 31 year old woman who was admitted with muscle pain and choloria 12 hours after physical exercise for a public contest, having mild SARS-CoV2 infection 3 weeks before. She was previously healthy, without regular use of any medication, in training for a physical test, with no family history of blood or muscle diseases. At admission she was dehydrated. Exams are shown in table 1. During hospitalization she was conducted with vigorous hydration, diuretics when necessary and urine alkalization, without hemodialysis. After 12 days, she was discharged. In outpatient follow-up, although the history fits as rhabdomyolysis after exercising physical activity in a post-covid patient, additional tests were performed:TSH 2,41 mU/L, negative serology for HIV, normal CRP and ESR. Despite negative family history of hemoglobinopathy, hemoglobin electrophoresis was compatible with sickle cell trait (HbA 25.7%, HbS 78%, HbA2 3.1%, HbF 17.8%, HbS 38.8%).

Discussion: Sickle cell disorder(SCD) is a genetic disease where hemoglobin (Hb) S mutation is present on at least one beta chain. When both β chains of HbA carry HbS mutation, the patient exhibits phenotypic features of SCD. If a mutation affects only one β globin chain and the other is normal, the patient is said to have sickle cell trait (SCT), which is a relatively benign carrier state and does not have the classic phenotypic features of SCD. It is estimated that affects 1 million to 3 million Americans, and 8 to 10 percent of African Americans, configuring a serious public health problem. SCT does not appear to be associated with increased overall mortality, but studies demonstrate that it is associated with a significantly higher risk of severe exertional rhabdomyolysis, and this case is a reminder to perform this assessment.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Kidney Involvement in Hantavirus Infection: The Importance of Kidney Biopsy
Daniel Lupusoru,1,2 Ioana Ailinciu,1 Georgiana Fratila,1 Mirece Lupusoru,2 Andreia G. Andrenoiu,1,2 Achim Camelia Adriana,1,2 Mihaela A. Banu,2 Gena Ismail,2,3* Institutul Clinic Fundeni, Bucharest, Romania;1Universitatea de Medicina si Farmacie Carol Davila, Bucharest, Romania.

Introduction: Hantavirus infection is, a rare zoonosis, associates two major syndromes: hemorrhagic fever with renal syndrome (HFRS) and cardiopulmonary syndrome (CPS). We present two cases of HFRS in which kidney biopsy (KB) was the key in guiding diagnosis.

Case Description: Case 1: 26-year-old female (no medical history) presented with acute kidney injury (AKI), nephrotic syndrome (NS), hematuria, high blood pressure (HBH), hepatic cytolyis, severe thrombocytopenia, anemia, leukocytosis, elevated LDH, normal haptoglobin, positive Coombs test, negative immunological and viral tests (C3/C4, ANA, ANCA, antiGBM, hepatitis B/C, HIV, Epstein-Barr, Cytomegalovirus), normal ADAMTS13 activity KB showed macroscopic features of hemorrhage in the renal medulla, light microscopy with normal glomeruli, proximal tubules with intratubular erythrocytes and recent hemorrhage in the medulla, electron microscopy with endotheliosis and interstitial inflammation, features suggesting Hantavirus infection. Serological testing of IgM/IgG antibodies (Ab) for Hantaan serotype (HTNV) established with endotheliosis and interstitial inflammation, features suggesting Hantavirus infection. The final diagnosis of HTNV hemorrhagic interstitial nephritis Therapy included steroids and Rapamir. Serum creatinine and liver enzymes returned to normal (Case 2: 30 year-old male (no medical history) presented with AKI, macroscopic hematuria, NS, HBP, and a normal appearing left kidney. The final diagnosis was Dobrava Hantavirus Hemorrhagic Interstitial Nephritis Therapy included steroids and 3 hemodialysis sessions with good evolution and correction of laboratory abnormalities.

Discussion: HFRS is most often caused by Dobrava and Puamula serotypes in Balkan Peninsula. Both presented cases live in the same rural area. Case 1 had positive serology for HTNV, usually found in China and Russia, but our patient didn’t travel abroad before she got ill. This emphasizes that HTNV nephritis remains an underdiagnosed disease and the need to re-evaluate geographic distribution of different strains. Both cases presented as thrombotic microangiopathies and KB had a decisive role in guiding diagnosis.

Case 2: 26-year-old female without medical history presented with AKI, macroscopic hematuria, NS, HBP, and a normal appearing left kidney. The final diagnosis was Dobrava Hantavirus Hemorrhagic Interstitial Nephritis Therapy included steroids and 3 hemodialysis sessions with good evolution and correction of laboratory abnormalities.

Conclusions: We finally conclude that an AKI alert system as implemented and followed-up in our study did not significantly improve clinical relevant endpoints in AKI subjects. Potential weaknesses were: (I) the lack of documentation of the time between receiving the alert and patient contact, (II) physicians in responsibility were not particularly informed about the alert system, (III) it is questionable whether serum creatinine is suitable for AKI alert systems in general.
AKI in Newborns with Infection, Including Sepsis, Detected by Novel Biomarkers

Joecilene d. Barbosa,1 Luis R. Castelo,1 Geraldo B. Silva Junior,2 Glaysson C. Meneses,1 Alice Maria C. Martins,1 Elizabeth D. Daher,1 Tiago L. Sampaio,1 Amanda d. Gomes, Paula Roberta de Lima,1 Nicole C. Lopes,1 Rosangela P. Machado,2 Romelia P. Lemes.1 Universidade Federal do Ceará, Fortaleza, Brazil; 2Universidade de Fortaleza, Fortaleza, Brazil.

Background: Acute kidney injury (AKI) is still poorly understood in newborns and hard to detect by traditional means. The aim of this study was to evaluate novel biomarkers in the early diagnosis of AKI in premature newborns (NBs) with infection, including sepsis.

Methods: This is a prospective observational study with 62 NBs admitted to a tertiary hospital in Fortaleza, northeastern Brazil, between August 2019 and September 2020. Using serum samples and urine, the biomarkers were measured by ELISA and compared to the determination of AKI by neonatal Kidney Disease: Improving Global Outcomes (KDIGO), by urinary output.

Results: No AKI was found by using the traditional biomarkers. CysC levels were 4.78 (1.9–25.63) mg/mg-Cr, uCysC 0.64 (0.2–2.29) mg/ml; uNGAL 27.81 (14.29–58.98) mg/mg-Cr; sNGAL 0.85 (0.4–1.39) mg/ml; and uNGAL 3.14 (1.74–5.51) mg/ml. In the group of sick NBs, the levels of CysC and uNGAL were associated with a longer period of hospitalization. As a consequence, after combining the two biomarkers, it was possible to observe a poor prognosis in NBs with neonatal infection or sepsis (AUC: 0.783; p = 0.016), Figure 1.

Conclusions: Our study evidenced that uCysC and uNGAL were associated with kidney injury in premature NBs with neonatal infection or early sepsis. Also, there was an association of uCysC and uNGAL with hospital stay time longer than 30 days and the prognosis of NBs.

Funding: Government Support - Non-U.S.

Figure 1. Urinary cystatin C and NGAL sensitivity and specificity for better prognosis for hospital stay time longer than 30 days. uCysC: urinary uNGAL: urinary lipocalin associated with neutrophilic gelatinase; AUC: area under the curve. Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of AKI and ARF on mortality in AECOPD patients.

Methods: We performed a retrospective, observational cohort study of data from Nanjing First Hospital. The effect of AKI and ARF on in-hospital mortality was assessed using a multivariable logistic regression model. Additional interaction was assessed with the relative excess risk due to interaction.

Results: 1647 participants were enrolled for analysis. Most (77%) patients were male, and the median age of the overall cohort was 78 years (IQR: 71 - 84). ARF and AKI occurred in 515 (31.3%) and 357 (21.7%) patients, respectively. Overall, in-hospital mortality was 75% (95% CI 72.1-77.3%). The in-hospital mortality rate of the ARF only group, the ARF only group, the AKI only group, and the group with both ARF and AKI group were 8.0%, 7.0%, 7.5%, and 29.9%, respectively. After multivariable logistic regression analysis, the independent risk factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.8-0.93, P = 0.001), ARF only (OR 8.53, 95% CI 3.64-19.99, P < 0.001), AKI only (OR 8.89, 95% CI 3.58-22.55, P < 0.001), and both ARF and AKI (OR 39.13, 95% CI 17.02-89.97, P < 0.001). The relative excess risk due to interaction was 22.62 (95% CI 0.31 to 44.93), the attributable proportion due to interaction was 0.59 (95% CI 0.36 to 0.79), and the synergy index was 2.46 (95% CI, 1.84 to 4.20), indicating ARF and AKI had a synergistic effect on in-hospital mortality.

Conclusions: ARF and AKI were independent risk factors for in-hospital mortality in AECOPD patients. Moreover, those two complications had a synergistic effect on in-hospital mortality.

PUB054
N-acetylcysteine and Contrast-Induced AKI: An Umbrella Review of Systematic Reviews

Background: There have been numerous trials and metaanalyses of N-acetylcysteine (NAC) in contrast-induced acute kidney injury (CI-AKI). The large trials do not demonstrate the futility of NAC. In this umbrella review, we synthesise the evidence as collated from the systematic reviews and metaanalyses.

Methods: A literature search was done to identify all systematic reviews on NAC and CI-AKI using databases from inception to end 2020. Two independent reviewers screened the studies and extracted data on including assessment of heterogeneity, publication bias and we used the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) to assess the risk of bias in the included studies.

Results: The literature search retrieved 273 citations, of which 42 systematic reviews were eligible. The quality assessment using the AMSTAR-2 was variable (see table) with high quality noted for certain domains (eg explicit question, explanation of study designs), low for others (funding, reasons and list of excluded studies). All studies reported high heterogeneity; 39/42 (93%) performed a meta-analysis, all with an overall benefit with NAC (pooled relative risks range 0.38 - 0.84). 26/42 (62%) reported on the presence of publication bias, and 31/42 (74%) reported the risk of bias. Only 2/42 studies (9%) reported on efforts to resolve heterogeneity did not report a summary effect size as a result.

Conclusions: Systematic reviews can provide misleading results if heterogeneity and publication bias are not taken into account.

AMSTAR Checklist
1. Was the research question and objective clearly stated?
2. Did the review authors include all studies that were eligible for inclusion?
3. How well was the risk of bias assessed?
4. Does the review authors estimate the risk of bias in each study included?
5. Did the review authors mention any significant sources of heterogeneity or bias?
6. Did the review authors assess the consistency of results?
7. Did the review authors assess the results of any sensitivity analyses?
8. Did the review authors discuss methodological quality?
9. Was there an adequate description of the search strategy?
10. Was there sufficient detail to assess the effect of excluding studies with high risk of bias?

PUB055
Nephrologist Interventions to Avoid Kidney Replacement Therapy in AKI
Jonathan Chavez,1,2 Jorge I. Michel gonzález,1,2 Andres E. De la torre quiruiga,1,2 Andres Aranda,1,2 Alecia X. Romero,1,2 Bladimir Diaz Villavicencio,1,2 Guillermo Garcia-Garcia,1 Universidad de Guadalajara, Guadalajara, Mexico; 2Hospital Civil de Guadalajara, Guadalajara, Mexico.

Background: We investigated the impact of early nephrology interventions on starting kidney replacement therapy (KRT), AKI progression and death in AKI patients.

Methods: In a prospective cohort, we followed-up for 10 days AKI patients. We analyzed 5 interventions of the nephrology team (fluid adjustment, nephrotoxic withdrawal, antibiotic dose adjustment, nutritional adjustment and removal of hypercatabolic solutions) and multivariate analysis for the risk of starting KRT (primary objective), AKI progression to stage 3 and death (secondary objectives).

Results: We analyzed 288 AKI patients. The mean age was 55.3 years, 60.7% were male, AKI KDIGO stage 3 was present in 50.3% of them, sepsis was the main etiology 50.3%, and 72 (25%) patients started KRT. The overall survival was 84.4%. Fluid adjustment was the only intervention associated with a decreased risk for starting KRT (OR 0.58, 95% CI 0.48-0.70, p = <0.001) and AKI progression to stage 3 (OR 0.59, 95% CI 0.49-0.71, p = <0.001). Receiving vasopressors and KRT were associated with mortality. None of the interventions studied was associated with reducing the risk of death.

Conclusions: In this prospective cohort study of AKI patients, early nephrologist intervention and fluid prescription adjustment was associated with lower the risk of starting KRT and progression to AKI stage 3.
PUB056
Acute Interstitial Nephritis (AIN): Current Presentation and Therapy
Beyond Corticosteroids (CS)

Background: AIN is most often caused by drugs (DI-AIN) and autoimmune disease (AI-AIN). Many patients (PTS) are treated with CS. There are sparse data on management of relapsing disease.

Methods: 53 PTS with AIN followed at our center between 2010-2020. Median (IQR) age was 55 years (31-64) at diagnosis and 28 (53%) were female. The cohort included 26 (49%) DI-AIN, 20 (38%) AI-AIN, 1 (2%) infection, and 6 (11%) unknown etiology. Antibiotics were the most common drug; Sjogren’s predominated AI-AIN. Table 1 summarizes the clinical course. Serum Creatinine (SCR) at biopsy was higher in DI-AIN. 4 (15%) DI-AIN were dialysis dependent at diagnosis vs. 0 AI-AIN. PTS (n=32, 62%). 44 (83%) PTS received CS as initial therapy, and DI-AIN PTS received shorter courses. 2 (8%) DI-AIN and 6 (30%) AI-AIN reached ESKD (p=0.06) after 66.5 (44.8-151.2) mo. Among SST patients not reaching ESKD, the follow up SCR 1.8 (1.6-2.2) mg/dl after 60 mo (30-114).

Conclusions: DI-AIN and AI-AIN continue to be the most common forms of AIN. DI-AIN PTS presented with worse renal function but were CS responsive. AI-AIN PTS were more likely to receive SST due to relapsing disease. 70% of SST PTS were with stable CKD after 60 mo. Further study in the role of SST in relapsing disease is warranted.

CUIMC AIN Cohort: Treatment Response and Outcomes

<table>
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<td>SCR at 24 mo</td>
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<td>SCR at 36 mo</td>
<td>1.7 (1.4-2.0)</td>
<td>1.05 (0.87-1.26)</td>
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Kidney function trajectory after stopping Olmesartan

PUB057
The Impact of Elective Withdrawal of Long-Term Concurrent RAAS Blockade in CKD Patients Presenting with Progressive AKI: A Prospective 40-Months’ Single-Unit Analysis
Macaulay A. Oniango, University of Vermont College of Medicine, Burlington, VT.

Background: There is consensus that RAAS blockade is renoprotective for both diabetic and non-diabetic proteinuric CKD. Nevertheless, there remains considerable debate and controversy regarding renal and cardiovascular (CV) outcomes with discontinuation of concurrent RAAS blockade in advanced CKD. Recent studies demonstrated discordant renal and CV outcomes.

Methods: In a Nephrology Office at the University of Vermont Medical Center, in Burlington, VT, USA, over 40 months, February 2018 – May 2021, concurrent RAAS blockade was electively discontinued in all patients who presented with progressive and >25% increase in baseline serum creatinine. Kidney function of this cohort was followed prospectively.

Results: 71 patients, 69 Caucasians, 1 African American and 1 Hispanic, 42:29 (M:F). Mean age 69.4 (37-95) years were treated. Medical co-morbidities included diabetes mellitus (37) and hypertension (66). They were mostly asymptomatic. Lisinopril was commonest agent in 40 (56%) patients. Mean duration of RAAS blockade before discontinuation was 2057 (112-4043) days. Baseline creatinine was 1.38 ± 0.49 (0.66 - 2.7) mg/dl, n=70. Peak creatinine was 2.31 ± 1.09 (1.1 – 8.3) mg/dl, n=67, P<0.0001, t=-6.4872, df=135. Nadir creatinine after drug discontinuation was 1.49 ± 0.45 (0.84 – 3.3) mg/dl, n=54, P=0.0001, t=5.1805, df=119. There were 5 (7%) deaths from nonrenal causes. Hyperkalemia in 34 (48%) and hyperphosphatemia in 13 (18%) resolved with improved kidney function.

Conclusions: The elective withdrawal of concurrent RAAS blockade in CKD patients who present with progressive worsening AKI generally demonstrate clearly improved renal outcomes. We posit that in selected CKD patients with progressive AKI such as in our study, RAAS blockade discontinuation indeed is the correct next step in their management for both improved renal and CV outcomes.

PUB058
A Case of Ayclovir Neurotoxicity Masquerading as Progression of Zoster Encephalitis
Jonathan Vincent M. Reyes, Arpita Joshi, Dawn Maldonado, Aaron S. Stern, Maritza Brown, Mount Sinai Health System, New York, NY.

Introduction: We present a case of varicella zoster virus (VZV) central nervous system infection complicated by acyclovir neurotoxicity.

Case Description: A 53-year-old male with ESRD on hemodialysis presented with acute encephalopathy. He had been diagnosed with VZV labyrinthitis in the 1980s. Symptoms include lethargy, confusion, visual hallucinations, dysarthria, myoclonus and death delusions. The diagnosis is clinical. Studies suggest a temporal association between symptoms and acyclovir administration as patients typically present within 24 to 72 hours; while VZV encephalitis patients present 1 week after the onset of skin eruptions. MRI findings for VZV encephalitis include clustered subcortical plaque-like lesions with mononuclear predominance and high protein. The pathophysiology for acyclovir neurotoxicity remains
under investigation. Currently the presumed mechanism is via high concentrations of 9-carboxymethoxymethylguanine (CMMG), a metabolite of acyclovir. Large doses of CMMG may inhibit mitochondrial DNA polymerase and alter mitochondrial function. Hemodialysis serves as the only treatment as the half-life of acyclovir in patients with ESRD can reach up to 20 hours, as compared to 3 hours in patients with normal kidney function. Acyclovir neurotoxicity poses a diagnostic dilemma since VZV encephalitis carries a mortality rate of up to 20%. Recognizing the risk factors and the temporal relationship between acyclovir administration and symptoms will lead clinicians to a timely diagnosis.

**PUB059**

**Severe AKI Leads to Worse Patient-Centered Outcomes in Survivors of Critical Illness**

**Víctor M. Ortiz-Soriano,** Kirby Mayer, Joshua Lambert, Javier A. Neyra.

1University of Kentucky, Lexington, KY; 2University of Cincinnati, Cincinnati, OH

**Background:** Acute kidney injury (AKI) is a detrimental condition that occurs in about half of critically ill patients. Survivors of critical illness are at high risk of persistent impairments in physical, cognitive, and emotional health, which may be worse in patients who suffered from AKI. The main objective of this study was to evaluate patient-centered outcomes of critical illness survivors who did and did not have severe AKI.

**Methods:** Retrospective observational study of adult patients surviving an ICU admission due to critical illness who attended outpatient follow-up in the ICU Recovery Clinic at the University of Kentucky. Patients with end-stage kidney disease were excluded. Patients were also excluded if they had an acute neurologic, traumatic, or orthopedic injury that prevented participation in outcomes testing at their follow-up visit. The primary outcomes were distance patient ambulated on the six-minute walk test (6-MWD) and self-reported health-related quality of life (HRQoL) in a visual analog scale ranging from 0 to 100 with higher scores indicating better quality of life at 3-month follow-up.

**Results:** A total of 105 patients were studied. Mean age (SD) was 54.6 (13) years, 53% were male, and 73% white. Sixty-eight (65%) patients had AKI, 46 of them severe AKI (KDIGO stage 2). ICU survivors that suffered from AKI stage 2 had lower HRQoL scores than those with AKI stage 1 or no AKI (69.1 ± 20.6 vs. 77.8 ± 14, p=0.015) and ambulated shorter distances on 6MWD (195.0 ± 153.8 vs. 300.0 ± 408.0, p=0.039). In multivariable regression analyses, older age, longer ICU length of stay, and AKI severity were associated with lower HRQoL scores; while older age and need for tracheotomy were associated with shorter distances achieved on 6-MWD.

**Conclusions:** Survivors of critical illness who suffered from severe AKI during their ICU stay had increased physical disability and worse quality of life compared to ICU survivors without severe AKI. Critical illness/AKI survivors may benefit from specialized post-ICU care and rehabilitation treatments. Future studies should focus on testing interventions that could ameliorate patient-centered outcomes in this special patient population.

**Funding:** NIDDK Support

**PUB060**

**High Symptom Burden in Medical ICU Patients with Any Degree of AKI**

**Sarah Ramey,** Yulin Yang, Holly G. Priegern, Khaled Abdel-Kader, James J Peters VA Medical Center, Bronx, NY; 2Weill Cornell Medicine, New York, NY; 3Vanderbilt University Medical Center, Nashville, TN; 4Icahn School of Medicine at Mount Sinai, New York, NY

**Background:** We know little about patients’ physical symptoms during acute kidney injury (AKI). Here we provide one of the first descriptions of symptoms in medical intensive care unit (MICU) patients with varying degrees of AKI.

**Methods:** This is a cross-sectional study from the MICU of an urban teaching hospital conducted 07/2016-01/2019. Study staff obtained informed consent from patients able to provide it or from a proxy (family member / friend) present at the bedside. Study staff then asked the patient or proxy if 12 specific symptoms had bothered the patient in the past 2 days. A nephrologist ascertained the presence and KDIGO stage of AKI at the time of study participation. This analysis excluded patients with end-stage kidney disease or a kidney transplant.

**Results:** Patient characteristics and symptom prevalence are shown in the table. In a linear regression model adjusting for AKI category, age, sex, race, ethnicity, reporter type, MICU length of stay, mechanical ventilation, and receipt of pressors / inotropes, only patient (rather than proxy) as symptom reporter was significantly associated with total number of symptoms (β=1.6, p=0.001).

**Conclusions:** MICU patients with any degree of AKI have a high symptom burden. The inability of most MICU patients to report their own symptoms might lead to underestimation of this burden.

**Funding:** Other NIH Support - NIA T32 AG049666 (SJR), NCI R35 CA197730 (HGP)

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Continuous variables as median (interquartile range); categorical variables as n (%).

*Some missing responses, so cell n may be less than column n.

**The 6 least-reported symptoms (vomiting, nausea, constipation, diarrhea, sweating, lack of appetite) not shown; P<0.10 for all.

**PUB061**

**Expanded Hemodialysis (HDx) May Improve Inflammation in AKI due to COVID-19 Disease Requiring Renal Replacement Therapy**

Giuseppe Gernone. ASL Bari, Bari, Italy.

**Background:** A baseline hyperinflammatory state afflicts COVID-19 positive patients (pts). AKI as a final common pathway of systemic inflammation and increased immunologic response leading to uncontrolled circulating levels of pro-inflammatory mediators and direct cytokine-induced organ damage. Hemodialysis expanded (HDx) represents a innovative strategy to remove uremic toxins up to 50 Kd, thanks to the medium cut-off membrane (MCO) and internal convection. Transcription of pro-inflammatory cytokines in peripheral leukocytes is markedly reduced and removal of soluble mediators of inflammation is enhanced by HDx. In vitro studies confirm that HDx limit neutrophil activation by decrease of ROS, TNF-alpha and IL6 and increase of apoptosis. Aim of this study is to evaluate the response to treatment with HDx and HF-HD in AKI due to COVID-19 disease.

**Methods:** Six pts were enrolled in a retrospective observational study. 3 pts were treated with HF-HD (FX80-Fresenius) and 3 with HDx (Theranova 400-Baxter) during COVID-19 infection. 2 pts treated with HDx and 1 with HF-HD showed hemorrhodynamic instability and need for vasopressors. They were daily assessed using the following: urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), D-Dimer and Albumin. The values have been reported as mean±SD.

**Results:** HDx (Qb=218±48 mL/min) discovered in every patient a significant reduction for CRP (-59.7% average) and PCT (-41.2% average), whereas HF-HD (Qb=205±27 mL/min) showed an opposite trend (+69.1% and +39.1% average). Moreover HDx induce a greater reduction of D-Dimer (51.4% vs 19.8% average), Urea and serum Creatinine in comparison to HF-HD (average),Tab.1 and better hemodynamic stability (Pam 75 vs 67 mm/Hg).

**Conclusions:** HDx effectively impact on inflammation and renal markers, compared to HF-HD, in COVID-19 positive. HDx, due to the increased clearance of cytokines, has recently been confirmed as a support for COVID-19 positive treatment in some Italian dialysis centers. Our preliminary results has to be confirmed by enlarged studies but in the meantime could help to build a new scientific evidence.

**PUB062**

**Enhanced Recovery After Surgery (ERAS) Protocol and the Risk of AKI**


**Background:** Two of the components of ERAS protocol are the maintenance of euvolemia and the use of multimodal analgesia, which includes NSAIDs. Given the restrictive fluid therapy strategy and the potential use of nephrotoxic analgesics, it’s pertinent to assess the risk and potential consequences of acute kidney injury (AKI). The objectives of this study are to assess the incidence of AKI and its outcomes.
**Mind the Gut: Gastric Complications of Immunosuppressive Therapy in a Patient with ANCA Vasculitis**

**Mariana A. Chang, Revekka Babayev, Stamford Hospital, Stamford, CT.**

**Introduction:** Granulomatosis with polyangiitis (GPA) is one of three ANCA-associated vasculitides which frequently affects the small vasculature of the pulmonary and renal systems. Management has evolved due to several pivotal trials, and recent data from PEXIVAS trial suggests lower prednisone doses maybe just as effective as the higher doses, with fewer complications.

**Case Description:** A 76-year-old - previously healthy woman presented with shortness of breath and cough. She was treated as an outpatient for presumed atypical bacterial pneumonia without improvement. On admission, she had a RR of 24 and oxygen saturation of 87% on room air and examination revealed crinkles in bilateral lung bases. Labs were remarkable for Hgb 7.1 mg/dL and Cr 4.2 mg/dL from a baseline of 1mg/dl. UA showed moderate blood and 100mg/dl protein. On day 2, she developed new-onset hemoptysis. Kidney function deteriorated over the next several days requiring temporary dialysis. She was started on empiric pulse dose steroids and kidney biopsy confirmed severe diffuse crescentic, necrotizing pauci-immune glomerulonephritis with anti-MPO antibody/P-ANCA sero-positiveity. She was treated with steroids and rituximab. She continued to have hemoptysis, prompting initiation of plasmapheresis as well as discharge on a 6-month course of prednisone. She was also discharged with GI prophylaxis, which unfortunately she was not taking and she was readmitted 1-month later for gastric ulcer perforation likely as a complication of steroid use, and unfortunately expired.

**Discussion:** This case outlines the severity and high risk for mortality in patients with GPA. Not only can the associated inflammation itself be fatal but immunosuppression is not without risk; such as the risk for peptic ulcer disease with steroid use as highlighted in this case. Data from trials such as PEXIVAS should be considered.
Conclusions: Systemic magnetic resonance imaging contrast treatment leads to the self-assembly of gadolinium-rich nanostructures in kidney tubular cells. These in vivo findings demonstrate that transmetalation is occurring (and this may be a mechanism for the resultant fibrosis) (Figure). Speciating the gadolinium-rich precipitates may aid in prophylactic strategies and therapies for gadolinium-induced diseases (including acute kidney injury, gadolinium deposition disease, gadolinium-associated plaques, ‘nephrogenic’ systemic fibrosis, and gadolinium-induced encephalopathy).

Funding: NIDDK Support, Veterans Affairs Support, Commercial Support - Dialysis Clinic, Inc.

PUB066
Scleroderma Renal Crisis Sans Scleroderma
Zachary Drury,1 Adhish Agarwala,1 Martin C. Gregory,1 Niraj K. Yadav,1 Monica P. Revelo Penafiel,1 Isaac Lloyd,2 Josephine Abraham.1 1University of Utah Hospital, Salt Lake City, UT; 2Intermountain Healthcare, Salt Lake City, UT.

Introduction: Scleroderma renal crisis (SRC) is an uncommon autoimmune disease that can present with hypertension, acute kidney injury (AKI), proteinuria, hematuria. Rarely is SRC the initial manifestation of scleroderma (scleroderma renal crisis sans scleroderma). We report a case of a patient presenting with SRC complicated by malignant hypertension, thrombotic microangiopathy, and acute kidney injury (AKI).

Case Description: A 47 year old female with four months of headache, blurry vision, and chest palpitations who presented to an outside hospital in hypertensive crisis. Serum Creatinine (Scr) was 1.1 mg/dl initially, however steadily increased to a peak level of 4.46 mg/dl. Urinalysis showed small blood and protein, and spot urine protein to creatinine ratio was 43.4/mg/ml with aldosterone/renin ratio 1.4. Evaluation for renal artery stenosis was negative. A kidney biopsy showed thrombotic microangiopathy with scattered subendothelial immune complex deposits. The patient was transferred to our facility where her Scr continued to worsen. She was started on Lisinopril 2.5mg when her creatinine level was 3.89 mg/dl. Scr stabilized after three days of ACE inhibition.

Discussion: SRC is a medical emergency requiring prompt diagnosis and treatment. Diagnosis can be challenging when this is the initial presentation of scleroderma. SRC should be considered in the differential diagnosis for patients presenting with AKI, new-onset microscopic hematuria, proteinuria, malignant hypertension and thrombotic microangiopathy. ACE inhibition is crucial for patient survival and can lead to renal recovery, which could take as long as 24 months after a renal crisis.

PUB068
Granulomatous Interstitial Nephritis Unrelated to Drug Exposure in a Patient with Ulcerative Colitis
Josoca O. Flores Santiago, Juan Carlos O. Velez, Muner Mohamed. Ochsner Medical Center - New Orleans, New Orleans, LA.

Introduction: Granulomatous interstitial nephritis (GIN) has been reported in patients with inflammatory bowel disease (IBD) treated with mesalamine but rarely as an inherent manifestation of IBD. Herein, we report a rare case of a young adult with a non-bloody diarrhea and acute kidney injury (AKI) caused by GIN and subsequently newly diagnosed with ulcerative colitis (UC).

Case Description: A 24-year-old man presented to an outside hospital with non-bloody watery diarrhea for 4 months, abdominal pain and unintentional weight loss. No report of voiding disturbance. He was taking no medications. Upon arrival, his vital signs and physical exam were normal. Laboratory data were pertinent for a serum creatinine of 8.0 mg/dl (baseline 0.6 mg/dl), and severe anemia. Urine studies were only relevant for sterile pyuria, no proteinuria. A kidney ultrasound showed no abnormalities. A kidney biopsy showed tubular injury. Possibility of fenofibrate-induced AKI was entertained, as he was not on any other potential nephrotoxic medications. The drug was stopped and renal function returned to his prior baseline within a month. It remains normal and unchanged 9 months after stopping the drug.

Discussion: It is known that fenofibrate can cause fully reversible isolated elevations in serum creatinine by inducing increased metabolic secretion of creatinine. It causes a true AKI by means of rhabdomyolysis, often when used with a statin, and in patients who have other risk factors like chronic kidney disease (CKD). However, there are recent studies showing fenofibrate causing true AKIs evidenced by rise in creatin C, an independent marker for kidney function, with subsequent decline in glomerular filtration rate (GFR). The exact mechanism of fenofibrate-induced AKI is still not fully understood but one hypothesis is that it impairs the production of renal vasodilatory prostaglandins, leading to renal vasoconstriction, and subsequently causing reduced renal plasma flow and glomerular pressure. Fenofibrate-induced AKI remains an under-recognized adverse effect of the drug. Although there is growing evidence and reports of these incidences, the exact mechanism remains unclear. Further studies showing the effects of fenofibrate on renal tissues at the molecular level are needed to better understand the pathophysiology of renal injury.

Serum creatinine (SCr) trend

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
biopsy was performed on the 9th day of hospitalization. He was discharged the next day.

He presented to clinic 6 days post-discharge with persistent diarrhea. His vital signs and physical examination remained normal. Serum creatinine was still elevated at 7.2 mg/dL. Microscopic examination of the urinary sediment only revealed coarse granular casts. The kidney biopsy specimen revealed a diffuse cellular infiltrate involving 80% of the interstitium, 70% interstitial fibrosis with atrophy, acute tubular injury and tubulitis. No glomerulitis was present for immunofluorescence. Electron microscopy showed no deposits. Treatment of GIN with prednisone 60 mg qd was begun. After 3 weeks, his serum creatinine improved to 4.8 mg/dL. A colonoscopy showed severe pancolitis consistent with UC and additional mesalamine and azathioprine were added. Six months later, his serum creatinine value remains at 4.8 mg/dL (eGFR 16 ml/min).

Discussion: GIN is a rare histologic diagnosis that may be the first manifestation of a systemic disease or caused by drugs. GIN causing AKI has been rarely described in therapy-naïve patients with IBD, primarily in Crohn disease. Given the potential for inflammation and young age and despite the severe chronicity in the biopsy specimen, the patient was treated with immunosuppressive therapy (IST). IST was later escalated to treat the UC lesion. Drug-naïve IBD should be listed as potential cause of GIN.

PUB071

Severe ESA Resistance Reversed by Cinacalcet in a Hemodialysis Patient with Sickle Cell Anemia

Peter N, Van Buren, Shani Shastri. The University of Texas Southwestern Medical Center Department of Internal Medicine, Dallas, TX.

Introduction: Hematologic diseases such as sickle cell disease (SCD) complicate anemia of end-stage renal disease (ESRD). Hyperparathyroidism is another etiology of ESA resistance that can cause irreversible bone marrow fibrosis. We present a case of severe anemia in a SCD patient on hemodialysis (HD) that dramatically improved with cinacalcet.

Case Description: The patient is a 28 year old Black man with SCD and ESRD from FSGS on thrice weekly HD. His anemia had been treated with hydroxyurea and high dose subcutaneous Aranesp (400 µg every 2 weeks) with a mean hemoglobin (Hgb) of 6.4 (1.4) mg/dL over several years. He developed worsening hyperparathyroidism on phosphate binders and vitamin D. Despite stable Aranesp doses, Hgb decreased until a blood transfusion was needed. Aranesp was increased to 500 µg every 2 weeks with some increase in Hgb. After starting cinacalcet, parathyroid hormone (PTH) decreased (1390 to 593 pg/mL), and Hgb further increased (8.2 to 11.2 mg/dL). Intermittent nonadherence to cinacalcet led to PTH variability until hospital admissions for sickle cell crisis and then COVID-19. Afterwards, PTH was more consistently suppressed. Following day 500, supplemental Epogen was given in addition to Aranesp, but Hgb increased only when PTH was most suppressed. During the first year on cinacalcet, there was a strong inverse correlation between Hgb and PTH (r = -0.6, p < 0.001). Figure 1 shows the Hgb, phosphorus, and PTH (divided by 150 to simplify y-axis) where Hgb peaks correspond to PTH nadirs.

Discussion: We demonstrate a case of severe anemia from both ESRD and SCD where Hgb dramatically improved with cinacalcet. We acknowledge that Aranesp increases preceded the initial Hgb rise, but Hgb peaks following PTH suppression exceeded any prior levels. These Hgb peaks were reproducible and sustained whenever PTH suppression was achieved. This case demonstrates that some hyperparathyroidism-associated ESA resistance may be reversible and supports how important control of bone mineral disease is in specific populations of HD patients that are susceptible to severe anemia.

PUB072

Addition of Roxadustat to Erythropoiesis-Stimulating Agent (ESA) Effectively Corrects ESA-Hyporesponsive Anemia in Peritoneal Dialysis Patients

Shunqi Dai, Chuan-Ming Hao. Huashan Hospital Fudan University, Shanghai, China.

Background: Erythropoiesis-stimulating agent (ESA) hyporesponsiveness is an important cause for the undertreatment of anemia. This study aimed to investigate the effectiveness and safety of adding HIF-PHI (roxadustat) to ESA for the treatment of ESA-hyporesponsive anemia in Peritoneal Dialysis (PD) patients.

Methods: This was a single-center prospective-designed study in PD patients of Huashan Hospital, Fudan University. Patients with ESA-hyporesponsive anemia were enrolled from January 2020 to April 2020 with a 24-week follow-up period. Patients were added to roxadustat at a starting dose of 50 or 100 mg thrice weekly without changing the ESA dose. Roxadustat and ESA dose adjustments were made as needed to maintain Hb levels within 11.0–13.0 g/dL. Efficacy outcomes and safety were assessed.

Results: A total of nine patients were recruited in the study. Both the cumulative responsive rate and the maintenance rate of patients with Hb>11g/dL were 100%. Six out of nine patients had ESA dose reduced from 15,000 UI/week or more to 7000 UI/week or less at week 24. No drug-related severe adverse event was reported in this study.

Conclusions: The present study showed that the addition of roxadustat not only overcome the corrected anemia in patients who were resistant to ESA, but also reduced the dose of ESA.

PUB069

Post Coronary Angiography Cholesterol Embolism Syndrome Resulting in Atheroembolic Renal Disease

Ravi Thakker, Anand Kumar, Abdul-Rehman Syed, Anjali Muraldehuran, Shancy Jacob. The University of Texas Medical Branch at Galveston, Galveston, TX.

Introduction: Cholesterol embolization syndrome (CES) has been characterized as a multi-system disease resulting from embolization of cholesterol crystal from arterial plaques. These emboli may cause ischemia in small arteries resulting in organ insula. A poorly recognized subgroup of CES is atheroembolic renal disease (AERD) or renal CES which accounts for a considerable subgroup. We present a case of a 69-year-old female who developed renal CES after undergoing coronary angiography.

Case Description: Our patient was a 69-year-old female with past medical history of chronic kidney disease stage 3, diabetes mellitus, hypertension, and heart failure with ejection fraction 40-45%, coronary artery disease, and chronic obstructive pulmonary disease who presented with progressive dyspnea and lower extremity edema for several months. Two months prior to this admission she had undergone coronary angiography. Her initial creatinine was 1.28 mg/dL. Over the next two months her creatinine up trended to 2.93 mg/dL. The inciting factor was initially attributed to acute kidney injury secondary to over diuresis. On examination the patient looked euvolemic but continued to have dyspnea and diuresis. Right heart catheterization was performed to better assess volume status which demonstrated normal filling pressures. Laboratory results were notable for persistent eosinophilia. In the context of recent contrast, rising eosinophilia, and normal filling pressures a renal biopsy was performed which demonstrated acute tubular injury, arteriopenhrosclerosis, and cholesterol emboli. Despite medical management, the patient’s renal function did not recover.

Discussion: Our patient’s initial presentation was concerning for decompensated heart failure with a possible cardiorenal insult. Post-diuresis instead of having improvement in her dyspnea and acute kidney injury, she continued to decompensate. Further complicating her presentation was recent contrast exposure for coronary angiography and rising eosinophilia. Biopsy ultimately showed cholesterol emboli that most likely dislodged post catheterization and caused acute tubular injury. The teaching point of our case is to consider atheroembolic renal injury irrespective of coronary angiography timing in patients with preexisting cardiac and kidney disease non-responsive to medical therapy.

PUB070

Checkmate! A Rare Case of Immune Checkpoint Inhibitor-Related AKI

Steffi Sathiyaraj, Daniel Varela, Leonardo Pozo Garcia, Sergio A. Trevino Manillo. The University of Texas Rio Grande Valley, Edinburg, TX.

Introduction: With the advent of immune checkpoint inhibitors (ICPIs) used in cancer therapy, there has been improved prognosis in various malignancies; however, with the use of these novel class of drugs, there has been a rise in associated immune-related adverse events reported, including acute kidney injury (AKI). ICPI-associated AKI is an emerging entity and in this case we highlight one such ICPI, Nivolumab, an antibody directed against programmed death-1, causing renal dysfunction.

Case Description: An 80-year-old man with renal cell carcinoma with baseline creatinine of .58 mg/dL (RCC) was referred to Nephrology services to evaluate AKI, with serum creatinine 2.3mg/dL, found in routine labs. The patient received immunotherapy with Nivolumab every four weeks. Urinalysis revealed no active sediment and renal ultrasound remarkable for solid mass in the left kidney, consistent with previous imaging of his RCC. The patient was diagnosed with Nivolumab-induced immune tubulointerstitial nephritis. At the time of presentation, the immunosuppression was placed on hold, and he was started on steroids. His kidney function gradually improved to serum creatinine of 1.3 mg/dL, with the withdrawal of Nivolumab and initiation of steroid therapy.

Discussion: In this case, we highlight an instance of Nivolumab-induced AKI, which poses a unique diagnostic and management challenge to clinicians due to lack of clinical awareness in account of the rarity of such immune-related side effects. With the rise in the use of new novel biologic agents, a multidisciplinary approach is essential so that clinicians can make a timely diagnosis when there is a high suspicion. Prompt discontinuation and early steroid therapy institution is crucial in management and can prevent further kidney injury or potential chronic kidney disease.
Hypercalcemia Secondary to Silicon Injections (Granulomatous Disease): Case Report

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Introduction: Hypercalcemia is a relatively common clinical problem. Among all the causes of hypercalcemia, primary hyperparathyroidism and malignancy are most common. Other less common causes include granulomatous diseases (tuberculosis and sarcoidosis), milk alkali syndrome, immobility, medications and familial hypercalcitropic hypercalcemia. We have seen a case of hypercalcemia secondary to silicon injections leading to granulomatus inflammation.

Case Description: 39 y/o F with a history of Sjogren’s disease (ANA 1:80 cytoplasmic, 1:2560 speckled, SSA/SSB + sicca symptoms), recurrent hypercalcemia, malnutrition, history of silicone injections (gluteal), at age 19, who presented to the hospital with facial swelling and found to have hypercalcemia (calcium 1.89, serum albumin 2.3). On examination she had severe soft tissue changes in her bilateral legs, ankles, buttocks and hips. Initial differential was malignancy, primary hyperparathyroidism and soft tissue tumor. Work up consistent with elevated 1,25-Vit D(280), ACE (77; mmol 9.67), PTHP (11.3; mmol 0.0-3.4) and PTH was found to be appropriately suppressed (<6.3; mmol 185-88). CT Scan reveal marked edema gluteal region bilaterally, pelvic wall, perineum and proximal thighs due to foreign body granulomatous/silicone injections. There was no evidence of malignancy on CT scans. She had no clinical signs of sarcoidosis. She has been treated with IVF, pamidronate, and calcitonin, with minimal improvement of her calcium levels. She continues to have recurrent hypercalcemia requiring steroids and repeat treatment with pamidronate. Hypercalcemia may persist, and long-standing low dose steroid recommended to maintain calcium and kidney function.

Conclusion: We diagnosed this patient with the granulomatous disorder secondary to silicon injections as the etiology of hypercalcemia. This is supported by her low parathyroid hormone (PTH) level and high (1,25) dihydroxy vitamin D level. Her Skin and soft tissue fragments from debridement/excision showed foreign body (silicone) granulomas, associated scarring and dystrophic calcification. Cosmetic filler injections are known to cause several acute and chronic effects, including local inflammation, nodule formation, and granulomatus reaction. Treatment includes steroids, bisphosphonates, and the removal of implants. Hypercalcemia may persist, and long-standing low dose steroid recommended to maintain calcium and kidney function.

Use of Alkaline Phosphatase as a Bone Marker in Patients on Hemodialysis

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Background: Some patients on hemodialysis may suffer from high turnover bone disease despite having levels of parathormone (PTH) within the targets set by KDIGO. Recent international guidelines suggest the use of other bone markers, such as serum total and bone-specific alkaline phosphatase (TALP and BALP respectively). The caveat of using TALP to assess bone turnover status is that other conditions, such as hepatic cholestasis, also cause increases in TALP. We can, however, use it as an alternative to BALP as long as gamma-glutamyl-transferase (GGT) is normal. Though it would generally be expected that PTH and TALP move in the same direction with changes in bone turnover, these two markers can sometimes evolve in opposite directions. Our study aimed to evaluate the correlation between PTH, TALP and BALP.

Methods: Cross sectional study including all patients on hemodialysis at the Hopital Maisonneuve-Rosemont from May 9, 2019 to June 7, 2019 (N=264 patients). We measured PTH, TALP and BALP in these patients and correlation coefficients were recorded. Regression analyses were performed for multiple potential confounding factors.

Results: The correlation between PTH and TALP was found to be positive and moderate (Rho 0.36; p-value < 0.0001). It was not statistically significant in patients having high GGT levels (above 60 IU/L) and was stronger in patients with normal GGT (Rho 0.40; p-value < 0.0001). The correlation between PTH and BALP was also positive and moderate, but stronger than with TALP (Rho 0.43; p-value <0.0001) and statistically significant even in patients having high GGT levels. The correlation between TALP and BALP was positive, strong and statistically significant (Rho 0.36; p-value <0.0001); it was stronger when GGT levels were normal compared to patients with high GGT levels (Rho 0.94 and Rho 0.71 respectively).

Conclusions: There is a positive correlation between PTH and TALP but it is only moderate. It is thus important to take into consideration TALP in patients with normal GGT levels when evaluating the bone status of patients on hemodialysis.

Correlation coefficients for all patients and stratified by GGT level
Haoxiongism: A Long-Term Case Report

Paricalcitol in Hemodialysis Patients with Secondary Hyperparathyroidism: A Long-Term Case Report

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Introduction: A case analysis of a HD patient with SHPT was performed, who was in paricalcitol treatment for 72 months, to provide a reference for SHPT management.

Case Description: A 67-year-old female HD patient had calcitriol 0.25 ug qd since 2014. On April 2015, biochemical indexes were Ca 2.02 mmol/L, P 2.1 mmol/L, iPTH 810.1 pg/mL, ALP 88 U/L, without significant abnormality in Parathyroid ultrasonography. While Coronary CT showed high-density calcified plaque in the left anterior descending branch, with a calcium score of 39. Then, she discontinued calcitriol and initiated Paricalcitol (Zemplar®) treatment (Detailed treatment regimen and indexes variations in Figure 1). On Month 24, iPTH level decreased to 176 pg/mL (78%), and the left anterior descending artery calcium Agatston score was 51. During Month 24-48, iPTH were 150-500 pg/mL, with stable Ca and P levels in normal range. On Month 72, the left anterior descending calcium Agatston score was 115 and a total calcium score of 147 (CT Images in Figure 2).

Discussion: Paricalcitol can selectively activate VDR especially in parathyroid, to correct the CKD-MBD and prevent cardiovascular events. In this long-term case, we have seen its efficacy and safety in SHPT treatment, especially in controlling the risk of vascular calcification. There is still a lack of data on the clinical application of paricalcitol for long-term use in China. Further studies are needed to confirm its benefit, and to explore best dosage for preventing vascular calcification in dialysis patients.

Figure 1 Variations in Biochemical Indexes

Figure 2 CT Images

Conclusions: This is the first national retrospective real-world observational study since intravenous paricalcitol is available in China since 2014. This study adds valuable information to real-world data investigating the use of paricalcitol in Chinese hemodialysis patients and demonstrated the use of paricalcitol as an effective and well-tolerated treatment for the control of PTH during its use in routine practice. The occurrence of hypercalcemia is mostly transient, followed by continuous treatment, the blood calcium level tends to be stabilized, and the blood phosphorus level will be improved with the control of PTH.

PUB078

A Missing Key or Faulty Lock: Use of an Alternative Vitamin D Analog Opens the Door to Success


Introduction: Secondary hyperparathyroidism is a complication of chronic kidney disease and characterized by high FGF-23 with low levels of 1,25-(OH)2-vitamin D due to low renal 1α-hydroxylase activity. Doxercalciferol requires 25-hydroxylation by the liver, a step preserved in end-stage kidney disease (ESKD), but may be subject to genetic polymorphisms that determine responsiveness. We present a case of secondary hyperparathyroidism resistant to high dose doxercalciferol but responsive to calcitriol.

Case Description: A 76-year-old man with ESKD due to diabetes on thrice-weekly hemodialysis with uncontrolled secondary hyperparathyroidism (intact parathyroid hormone (iPTH) 1348 pg/mL) was started on a calcium-based phosphate binder and doxercalciferol 1 mcg IV three times a week. Doxercalciferol was titrated to 20 mcg three times a week, an equivalent calcitriol dose of 19 mcg/week, but his secondary hyperparathyroidism remained poorly controlled (iPTH 732 pg/mL, corrected calcium (cCa) 8.0 mg/dl., phosphorus (P) 5.1 mg/dl). He had normal liver function and did not take CYP3A4 inhibitors. He was changed to calcitriol 0.5 mcg daily with dramatic improvement over three months (iPTH 247 pg/mL, cCa 9.2 mg/dl, P 3.3 mg/dl).

Discussion: We highlight the use of an unusually high dose of doxercalciferol (~2 mcg per week) resulting in suboptimal iPTH and calcium response. This dose is significantly higher than the annual mean IV doxercalciferol dose of 112 mcg per patient (~2 mcg per week). Our patient had a rapid reduction in iPTH and normalization of cCa using a relatively low dose of calcitriol. Unlike calcitriol, doxercalciferol lacks a 25-OH group requiring activation by hepatic 25-hydroxylase. A deficiency, or loss of function in this key enzyme, is a rare polymorphism seen in vitamin D dependent rickets type 1B, usually treated with 25-OH-vitamin D, but needs 1α,25-(OH)2-vitamin D in ESKD. Alternatively, genetic variation of the vitamin D receptor-ligand binding domain may reduce its affinity for some vitamin D analogs. Clinicians should suspect potential polymorphisms at fault when high doses of vitamin D analog are used with inappropriate response. We recommend switching vitamin D analogs and consider genetic testing. Characterizing vitamin D receptor protein polymorphisms may influence prescribing practices of vitamin D analogs in the future.

PUB079

Persistent Severe Hyperparathyroidism After Parathyroidectomy

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Introduction: Parathyroidectomy is the definitive treatment for secondary hyperparathyroidism (SHPT) refractory to medical management. We report a case of persistent severe hyperparathyroidism after subtotal parathyroidectomy in a hemodialysis patient.

Case Description: A 35-year-old male with ESRD on HD due to idiopathic membranous nephropathy presented with progressive fatigue and bone pain. PTH was 3709 pg/mL, Phos 9.7 mg/dl, Ca 10 mg/dl, and ALKP 919 IU/L, in the setting of noncompliance with his medications, including cinacalcet, calcitriol, and sevelamer. He was transitioned to IV etelcalcetide given at HD, but had poor response, with PTH levels between 2000-4000. After discussion, he opted for parathyroidectomy. Preoperative
sestamibi scan demonstrated a focus of increased uptake in the lower right thyroid lobe without a corresponding mass. Intraoperatively, the bilateral inferior parathyroids appeared nodular and were removed. Surgical pathology confirmed nodular hyperplasia. The normal-appearing left superior gland was autotransplanted to a subcutaneous pocket. Despite extensive exploration of the retroesophageal space and carotid sheath, the right thyroid lobe gland could not be located, so a right thyroid lobectomy was performed.

Intraoperative PTH (iPTH) levels were 2612 μg/ml before reset, 519 μg/ml at 10 minutes post-reset, and 560 μg/ml at 20 minutes. The patient had severe postoperative hypocalcemia which responded well to calcium supplementation. However, by post-operative day 8, his PTH had rebounded to 2524 μg/ml.

Discussion: Persistent hyperparathyroidism has been defined as PTH elevation developing within 6 months of surgery despite adequate iPTH drop. Prior case series have attributed this to the presence of missed ectopic or supernumerary glands, although these are uncommon situations that typically take weeks to months. Despite an initial >75% reduction in iPTH after 10 minutes, our patient’s rapid return to preoperative PTH levels is atypical, and is concerning for the concurrent development of tertiary HPT in his residual parathyroid tissue. These observations suggest that a history of longstanding secondary HPT may lead to poorer outcomes after parathyroidectomy.

PUB080
Hospitalization Is Related to Osteoporosis in CKD Patients: Data from the Brazilian Registry of Bone Biopsy (REBRABO)
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Background: Mineral and bone disorder (MBD) is related with chronic kidney disease (CKD) and associated with significant morbidity and mortality. REBRABO database contains clinical, laboratory and histological information about Brazilian CKD patients with MBD. The relationship between the type of renal osteodystrophy (RO) and clinical outcomes is unclear.

Methods: This is a national, observational and prospective clinical study. Clinical, demographics, laboratory and bone histology data were collected from CKD patients between Aug/15-Dec/18. Patients were followed by five years and clinical outcomes such as bone fractures, hospitalization and death were registered.

Results: Data from 179 patients who were submitted to bone biopsy were analyzed. Patients aged 52±12 years, 93 (52%) men and 80 (45%) white; 133 (85%) patients were under hemodialysis treatment. Serum intact parathormone, alkaline phosphatase, calcium, and phosphate levels were 456 (63-514) μg/mL, 174 (73-205) IU/L, 9.2±1.7 mg/dL and 5.6±1.7 mg/dL, respectively. Osteitis fibrosa, mixed uremic osteodystrophy, adynamic bone disease, osteomalacia and osteoporosis occurred in 69 (39%), 39 (22%), 59 (33%), 7 (4%) and 82 (47%), respectively. The average follow-up time was 1,318 days; during follow-up 19 bone fractures, 61 hospitalizations and 47 deaths were detected. However, diagnosis of osteoporosis was related with hospitalization (p=0.03).

Conclusions: Osteitis fibrosa was the most prevalent type of RO in our sample. A high prevalence of osteoporosis was detected and related with increased hospitalization. Type of RO apparently is not related with outcomes.

PUB081
A Case of Tumor-Induced Osteomalacia (TIO) with Paradoxical Fibroblast Growth Factor 23 (FGF-23) Response After Surgical Excision Shab E Gul,1 Eric W. Tang,2 Jei Tang.1,2 Harvard College, Cambridge, MA; 3Lifespan Health System, Providence, RI; 4Brown University Warren Alpert Medical School, Providence, RI.

Introduction: Primary hyperparathyroidism is a strong risk factor for calcium kidney stone (CKS) formations. However, the kidney stone effect from normocalcemic hyperparathyroidism have not been described. Here we present a case series of six recurrent CKS formers who had elevated plasma parathyroid hormone levels with normal serum calcium concentration. All of them underwent nuclear imaging of the parathyroid glands. Relevant features consistent with parathyroid adenoma and underwent subsequent resections of the adenoma. We compared pre- and post-operative 24-hour urine calcium (UC) and phosphorus (UP) standardized by urinary creatinine, as well as changes in kidney stone burden assessed 2-12 months after the surgery. All patients included in this report were instructed to maintain their diet before and after the surgery.

Case Description: Of these six stone formers, three were men, and the mean age was 60 years. All had vitamin D deficiency with normal serum 1,25-(OH)₂-vitamin D. Two had hypertension. Two others had dyslipidemia. All of the three who had DEXA scans had osteopenia, all had osteoporosis. Mean serum calcium was 9.8±0.8 mg/dl, mean serum phosphorus was 3.0 mg/dl. Five had baseline 24-hour UC >240 mg (median 309 mg), one had normal 24-hour UC (186 mg). 24-hour UP ranged from 663 mg to 1672 mg. None of them were prescribed with thiazide diuretics, calcium containing supplements or medications that could affect phosphorus absorption during the study period. After partial parathyroidectomy, mean serum calcium reduced by 0.75 mg/dl, mean serum phosphorus increased by 0.1 mg/dl, and neither serum 25-(OH)-vitamin D nor 1,25(OH)₂-vitamin D changed significantly (mean, -0.8 mg/ml, +0.7 mg/ml, respectively). For the urinary studies, two had increases in UC (mean 61 mg, 18%), four had reductions in UC (mean -23%, 9%). One had an increase in UP (349 mg, 53%), five had reductions in UP (mean -244 mg, -19%). Of the five patients who had kidney ultrasound performed before and 2-12 months after the surgery, four had increases in the post-operative stone burden (mean +43%), one had a 100% reduction.

Discussion: In this small series, normocalcemic hyperparathyroidism did not appear to have a consistent effect on the risk of calcium kidney stone formation.

PUB083
Misregulation of Interstitial Matrix Fiber Patterning in a Model of Stromal Cell Abnormalities
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Background: Murine kidney interstitial extracellular matrix (ECM) is a network of proteins and glycosaminoglycans outside cells. The ECM forms intricately patterned fibers in the developing kidney capsule, vertically aligned in the cortex, and surrounding the medullary rays. Forkhead box D1 (Foxd1) cells synthesize interstitial matrix and are required for kidney stromal cell patterning of the nephron; however, the role of Foxd1 in interstitial ECM fiber patterning has not been investigated.

Methods: Murine embryonic day (E)18.5 Foxd1 knockout (Foxd1−/−) kidneys were decellularized with sodium dodecyl sulfate, fixed and stained for ECM proteins, and rendered in 3D.

Results: Vertical fibers were abnormally, perpendicularly aligned relative to the branching nephron in Foxd1−/− kidneys (open arrow), suggesting Foxd1 is important for stromal cell orientation of interstitial ECM (Figure 1). However, the organization of capsule and fibers around the medullary ray sheath was maintained when compared to Foxd1+/+ controls.

Conclusions: Kidney interstitial ECM dramatically changes with development. Abnormalities in the vertical fibers in the Foxd1−/− mouse correlate with the loss of the nephrogenic zone, suggesting the fibers are involved in nephron morphology development.

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medullary ray sheath fibers (*, E-F) appear retained in the Foxd1-/-(B-B) kidneys. Vertical fibers were maintained. (A-A) Control kidneys showed vertical fibers (closed arrow) (green = COL26A1) aligned parallel to the developing nephron (FREM2 = blue, WGA = red). (B-F) In the Foxd1-/+ kidneys, the vertical fibers (closed arrow) were present, but some vertical fibers were abnormally perpendicular to the nephron (open arrow). (C-F) POSTN* (green) capsular fibers (arrowhead, C-D) and medullary ray sheath fibers (*, E-F) appear retained in the Foxd1-/+ kidney. Scale bar = 100 µm. 25x confocal z-stacks 590 × 590 x 171 µm (A-B''), 57 µm (C-F).
for 8 weeks. The rats were euthanized and the kidneys stored at -80°C. We analyzed the metabolic and respiratory profiles (NO, for nitrosative stress), TBARS (an indirect measure of oxidative stress, OS) and renal function in plasma and urine. The results were described as mean ± SE, p < 0.05.

Results: Viability was 100% in all HMC groups; there was a significant increase in cellular NO levels with pentoxifylline (PTX) expression in HGI group, which were reduced with EA. In DM rats EA reduced glycemia and normalized other metabolic parameters, in addition to improving renal function and OS after 3 days, 4 and 8 weeks of treatment, being the more prolonged treatment, more effective. The histology analysis showed that EA reduced structural lesions of the renal cortex such as diffuse sclerosis and glycosidic degeneration, in DM animals.

Conclusions: The consumption of EA could contribute to a better control of OS associated with the reduction of inflammatory factors, suggesting the importance of these bioactive compounds as non-pharmacological adjuvants, to delay the complications in diabetic patients.

Funding: Government Support - Non-U.S.

PUB087

Pentoxifylline in Diabetic Kidney Disease (VA PTXRx): Protocol for a Pragmatic Randomized Controlled Trial

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Background: Diabetic kidney disease (DKD) is the most frequent cause of end-stage renal disease (ESRD) in the U.S. and worldwide. Recent experimental and clinical data suggests that the modulation of the phosphodiesterase inhibitor pentoxifylline (PTX) may decrease progression of kidney disease. However, a large-scale randomized clinical trial is needed to determine whether this agent can reduce ESRD and death in patients with DKD.

Methods: VA PTXRx is a pragmatic, randomized, placebo-controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the time to ESRD or death in type 2 diabetic patients with DKD when compared to usual care plus placebo. The study aims to enroll 2510 patients over a 4-year period with an additional up to 5-year follow-up to generate a total of 646 primary events. The primary objective of this study is to compare the time until ESRD or death (all-cause mortality) between participants randomized to PTX or placebo.

Secondary endpoints will be: (1) Health-related quality of life, (2) Time to doubling of serum creatinine, (3) Incidence of hospitalizations for congestive heart failure (CHF), (4) Incidence of a three-point major adverse cardiovascular events (MACE) composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) Incidence of peripheral vascular disease (PVD), (6) Change in urinary albumin-to-creatinine ratio (UACR) from baseline to 6 months, (7) Rate of annual change in estimated glomerular filtration rate (eGFR) during the study period.

Funding: VA PTXRx is supported by the U.S. Department of Veterans Affairs, the V andenberg,1 Plantinga.1

Trial Registration: This study is registered with clinicaltrials.gov (Identifier: NCT03625648)

Results: Study enrollment began in November 2019. Through April 2021, 146 patients have been randomized during the ramp-up phase of the study.

Conclusions: PTX is a readily available, safe, and inexpensive medication which might be effectively repurposed to treat DKD.

Funding: Veterans Affairs Support

PUB088

Perceptions of Care Coordination During and After Hospitalization Among Patients Receiving In-Center Hemodialysis

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Background: In the United States, 34% of hospital discharges among patients receiving dialysis are followed by a 30-day unplanned readmission. As part of an ongoing pilot study (DialysisConnect), we examined the perceptions of patients receiving hemodialysis (HD) regarding care coordination between providers at the hospital and dialysis clinic.

Methods: Our study targeted all 113 patients receiving in-center HD who were being treated at one of four dialysis clinics and had been hospitalized at a single hospital in Atlanta, Georgia, in the prior 6 months. We administered a one-time survey about their care coordination during their hospitalization episode and used descriptive statistics to summarize the results.

Results: Respondents (n=24, 21% response rate) had an average age of 62 years, 100% were Black, 46% were male, and on average patients had been receiving HD for 4 years; non-respondents were similar in terms of demographics. The percentages of patients who reported that their hospital and dialysis providers knew key information or performed care coordination tasks during and after hospitalization were generally high (Figure). Most patients reported that hospital providers asked about their reason for hospital stay (79%), dialysis schedule (75%), symptoms (75%), current medications (71%), vascular access (67%), nephrologist name (67%), dialysis facility name (54%), and body weight (50%). Only half (48%) brought discharge instructions to the next outpatient HD session.

Conclusions: Most patients (62-91%) perceived that both hospital and dialysis providers were aware of the patient’s clinical situation and had exchanged necessary necessary information from active patients. Results from actively engaging in care coordination. Future efforts to improve coordination of care between dialysis clinics and hospitals should target not only providers in both settings but also patients and their healthcare surrogates.

Funding: NIDDK Support

PUB089

Leptin Levels and Appetite Score in Patients on Hemodialysis Using High Flux or Medium Cut-Off Membranes

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Background: Chronic kidney disease (CKD) patients on hemodialysis may have a modified appetite due to several factors including a lack of uremic toxins elimination. The use of new dialysis membranes, such as medium cut off (MCO) has been suggested as an alternative to improve the removal of toxins, especially those of medium and high molecular weight. This study aimed to evaluate if the use of the MCO membrane would decrease toxin levels, particularly leptin and improve the appetite of CKD patients on hemodialysis program.

Methods: This is a pre-defined exploratory analysis of a randomized, open study, with a crossover design of 28 weeks of follow-up, which compared the effects of MCO and high flux membranes in 32 CKD patients on hemodialysis. Appetite assessments were performed using the Appetite and Food Satisfaction Questionnaire (AFSQ).

Results: The high-flux group had an appetite score of 3.25 ± 3.62 and 2.80 ± 3.14 at the beginning and at the end of treatment period, respectively, and the MCO group 3.62 ± 3.21 and 3.26 ± 3.28. There were no effects of treatment (p = 0.573), time (p = 0.376) and interaction (p = 0.770) between the high-flux and MCO groups. Leptin levels, at the beginning and at the end of the treatment period, were 2.47 ± 1.57 and 2712.72 ± 1.54 μg/L in the high-flux group and 2.45 ± 1.65 and 2.78 ± 1.62 μg/L in the MCO group, respectively.

There was a time effect (p = 0.014), showing an increase in leptin levels in both groups, while treatment (p = 0.771) or interaction (p = 0.218) effects were not observed.

Conclusions: There is no difference between the effects of MCO or high flux membranes on leptin levels or appetite of CKD patients in hemodialysis during the study.

Funding: Private Foundation Support

PUB909

Can Restoration of Heart Rate in ESRD Lower Brain Natriuretic Peptide?

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Introduction: Brain Natriuretic Peptide (BNP), is predominantly produced by the left ventricular (LV) myocytes. BNP’s production is triggered in response to stretch of the left ventricular myocytes by either increased volume or pressure within the LV cavity. Elevation of BNP is induced by bradyarrhythmia and high degree atriointerventricular block. We describe a case of a dialysis-dependent patient presenting with complete heart block with an elevated BNP from his baseline and review whether correcting the rhythm problem resulted in correction of his BNP.

Case Description: 98 yr old male with ESRD receiving maintenance hemodialysis presented with shortness of breath and decreased heart rate. He reported shortness of breath on ambulation but denied chest pain, increased swelling, or any other symptoms. Heart rate (HR) was 40 bpm and blood pressure 138/52 mm Hg. Electrocardiogram (ECG) revealed a complete heart block, the chest x-ray did not reveal any acute cardiopulmonary abnormalities. BNP was 2667 pg/mL. Cardiac pacing pads were placed in the Intensive Care Unit while planning for permanent pacemaker placement. He remained hemodynamically stable with HR in the 30s-40s bpm and a dual-chamber pacemaker was placed 24 hr later. Symptoms of dyspnea improved after the procedure with a paced rhythm of 60 bpm. BNP repeated 90 min after the procedure remained...
Discussion: Our patient provided a unique opportunity to differentiate between the effects on BNP of an improved cardiac output with restored cardiac rhythm versus changes in intravascular volume. This case demonstrates that this anuric patient’s rhythm restoration was not sufficient to lower BNP values, while ultrafiltration did. Thus, we seem to be able to confirm that, it is solely the volume status that affects BNP value, not the cardiac rhythm or cardiac output.

**PUB091**

Temporal Changes in Physiology During Inpatient Hemodialysis Sessions

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Background: Patients receiving maintenance hemodialysis (HD) in the United States have an average of 1.6 admissions per year (~700,000 inpatient HD sessions). Little is known about the temporal changes in laboratory values, ECGs, and volume status during HD sessions in these vulnerable patients.

Methods: We performed a prospective cohort study (n=30) of hospitalized HD patients to measure serum laboratory concentrations (electrolytes, blood gases, and ionized calcium levels), ECGs, and ultrasonographic measures of volume status (8-zone lung images for the number of B-lines and internal jugular vein diameter) pre-, one hour into, and post-HD during one inpatient HD session. Ultrasound images were analyzed offline by a core imaging laboratory blinded to clinical information and imaging time point.

Results: The mean age of participants was 62 years. 53% were male and 43% were Black. Serum chemistry levels were dynamic, with the most rapid changes occurring within the first hour for all biomarkers (Figure 1). The median increase in QTc duration on ECG (post-HD QTc minus pre-HD QTc) was 7.5 [5-19] msec. Though the sum of pulmonary B-lines decreased from pre- to post-HD (median decrease: 5 [1-6.5], p=0.02), internal jugular vein diameter did not change (p=0.73).

Conclusions: Among hospitalized patients undergoing HD, there are dynamic changes in serum chemistry parameters, QTc durations, and volume status during their HD sessions. Further research is required to assess how variations in these changes during HD are associated with clinical outcomes and whether HD prescriptions can be tailored to optimize patient care.

**PUB092**

Predictors of Mortality in Hemodialysis Patients in a Large Dialysis Network in India


Background: Mortality of HD pts is influenced by age, comorbidity, dialysis, facility and socioeconomic factors. With much unknown regarding MHD mortality in India, we aimed to study the incidence and factors predicting mortality in a large dialysis network in India.

Methods: Consecutive deaths, Jan 1 to March 31, 2021 in a HD network were reviewed for age, gender, HD freq., vascular access, Hb, comorbidity, MHD duration, payer type, educational status, and BMI. An age stratified matched control was used to compare factors using t test and Chi squared test. Binary logistic (uni & multi) was used to identify risk factors associated with death. Significance: 5%. SPSS ver 26 was used.

Results: 797(4.8%) deaths occurred among 16516 patients. Table 1 shows pt characteristics. Simple logistic regression: Tier III city, <6 mon HD, public Insurance, ↓ Hb, temporary access, Kt/V <1.2, Alb <3.5, DM, h/o MI and hospitalization <3 mon had significant OR (not shown). Multiple logistic regression showed OR for illittracy: 2.7 (1.7-4.4), secondary school: 1.7 (1.1-2.5), public insurance 2.3 (1.3-3.8), <1 mon on HD: 2.3 (1.3-4.4), temporary catheter:1.7 (1.3-2.7), Alb <3.5 g/dL; 2 (1.3-3.8), ↓ Hb 2.9 (1.5-5.9), DKD: 1.5 (1-2), HD in PPP centre: 2.1 (1.3-3.2) and hospitalizations <3 mon: 4.7 (3.3-6.6) were significant.

Conclusions: Mortality is high in MHD pts in India and is associated with temp access, ↓ Alb, ↓ Hb, recent hospitalization, DM, ↓ age, eduction & public Insurance status.

Table 1: Characteristics of patients who died Jan 1 to March 31, 2021 (n=797)

**PUB093**

A Multicenter, Retrospective, Observational Study of Dialysis Facility-Level Hyperkalemia Burden in China: Rationale and Design of the Visualize-HD Study

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Background: Hyperkalemia (HK) is a deadly complication in patients (pts) undergoing hemodialysis (HD), accounting for about 1/4th of emergent dialysis treatment. Excess mortality and hospitalization have been associated with HK, especially after the long (2-day) interdialytic interval (LIDI) in thrice-weekly HD pts compared with the short (1-day) intervals. Research on disease burden, risk factors and association of HK and mortality in Chinese pts is scanty.

Methods: This multicenter (300 HD centers), observational study will involve Chinese patients with chronic HD from eastern, central and western parts of China (except Hong Kong, Macao and Taiwan) (Figure 1). HD centers having >100 chronic pts (<3 mons on HD) within 3 years before study initiation, participation willingness, having routine blood collection post LIDI and death records will be included. Pooled data (at HD facility-level) about pts characteristics, hk levels, dialysis prescriptions on facility practice patterns, and death records will be collected retrospectively.

Results: The primary and secondary endpoints will be to examine the association between suspected risk factors and HK-proportions and to describe HK burden respectively. Suspected risk factors include dialysis and Sk testing frequency; patient characteristics and medication usage. The constitution ratio of different sK levels after practice patterns, and death records will be collected retrospectively.

Results: The primary and secondary endpoints will be to examine the association between suspected risk factors and HK-proportions and to describe HK burden respectively. Suspected risk factors include dialysis and Sk testing frequency; patient characteristics and medication usage. The constitution ratio of different sK levels after practice patterns, and death records will be collected retrospectively.

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Results: The primary and secondary endpoints will be to examine the association between suspected risk factors and HK-proportions and to describe HK burden respectively. Suspected risk factors include dialysis and Sk testing frequency; patient characteristics and medication usage. The constitution ratio of different sK levels after practice patterns, and death records will be collected retrospectively.
**PUB094**

**Predicted Rebalancing of Sodium in a Sorbent Dialysis System**


**Background:** The Dially Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test sodium ion rebalancing in a 125L circulating volume over 270 minutes using a predicted alkali infusion to maintain a Na concentration of approx. 140 mEq/L.

**Methods:** A 125 L volume of dialysate was circulated at approx. 400 mL/min & 37 C through a sorbent filter. It is expected that with each pass through the filter the dialysate will be depleted of electrolytes and sodium [Na] and pH will lower. Dialysate is refurbished with an additional infusion of Ca, Mg and K salts. Based upon the predicted [Na] profile another pump will infuse an alkali solution at a varying rate to maintain the final [Na] at approx. 140 mEq/L. The experiment is continued until breakthrough occurs or the infusate outlet reaches 10 ppm of NH₄.

**Results:** The [Na] over 270 mins are depicted in table 1. TP1, the [Na] of the dialysate taken prior to passing through the sorbent filter after leaving a stirring tank containing 150L of dialysate was 137.9 – 143.4 mEq/L. TP2, the [Na] in the fluid upon leaving the filter was an average of 129.5 mEq/L ranging from 119.1 – 136.0 mEq/L. TP3, the [Na] in the dialysate after refurbishing with an alkali solution prior to reentering the stirring tank was an average of 139.3 mEq/L ranging from 138.1 – 143.4 mEq/L.

**Conclusions:** The results validate the ability to maintain dialysate sodium balance over the dialysis period using a sorbent filter while refurbishing dialysate with a predicted alkali infusion.

**Funding:** Commercial Support - Diality Inc

**Table 1:**

<table>
<thead>
<tr>
<th>Component</th>
<th>Conc (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140</td>
</tr>
<tr>
<td>Ca</td>
<td>5</td>
</tr>
<tr>
<td>Mg</td>
<td>1</td>
</tr>
<tr>
<td>K</td>
<td>3</td>
</tr>
<tr>
<td>NH₄</td>
<td>14</td>
</tr>
<tr>
<td>pH</td>
<td>7.00</td>
</tr>
</tbody>
</table>

**Figure 1:**

**Figure 2:**

**PUB095**

**Bicarbonate and pH Maintenance in a Sorbent Dialysis System**


**Background:** The Dially Hemodialysis Machine is designed for a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One of the modalities uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: Demonstrate bicarbonate and pH can be balanced with an alkali infusion.

**Methods:** Dialysate volumes of 125 L were circulated at approx. 414 mL/min & 37 C through a sorbent filter. The starting dialysate concentrations for electrolytes, pH and Urea are provided in table 1. The dialysate will be regenerated by an infusate solution containing Ca, Mg and K salts. In the first experiment a predicted [Na] profile pump will infuse an alkali solution at a varying rate to control the final [Na] at approx. 135mM. A second experiment a constant infusion of the same alkali was used as a reference. The total bicarbonate buffer was measured by titration. The pH was measured by a laboratory grade probe.

**Results:** The total bicarbonate buffer as alkalinity for an experiment with a constant infusion of alkali is compared to an experiment with varied infusion of alkali (controlling outlet sodium) in Figure 1. The same two experiments also show pH data in Figure 2.

**Conclusions:** The results show that the alkali infusion can simultaneously balance alkalinity and pH in a sorbent system using this infusion to maintain sodium at a set point.

**Funding:** Commercial Support - Diality Inc

**Table 1:**

**PUB096**

**Effect of Hemodialysis Rounding Report Availability on Hospitalized ESRD Patient Parameters**

Khalid Elharrif,1,2 Nidal Alhosainat,2 Petersen Greti,1 Ratha V. Kulasingam,1 Omar S. Al-Taweel,1 Hania Kassem.2 1Kern Medical Center, Bakersfield, CA; 2The University of Texas Medical Branch at Galveston, Galveston, TX.

**Background:** Each ESRD patient has a rounding outpatient HD report which is established by the outpatient dialysis unit and contains pertinent information including dry weight (EDW), dialysis prescription, and current medications. In this study, we compared the outpatient dialysis-related parameters between 2 groups of patients, those for whom rounding reports were made available and those whose reports were not able to obtain.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

793
Methods: The outpatient hemodialysis facility list was available for all healthcare providers. The facilities were contacted to obtain the hemodialysis report for the hospitalized patients with ESRD. The relevant parameters were obtained from these reports, which included hemoglobin, phosphorus, and EDW. The aforementioned identical parameters were monitored during the course of the hospitalization on all ESRD patients. Patients with available outpatient dialysis reports were restarted on the same outpatient doses of Epogen, phosphate binders, and EDW was adjusted to the same outpatient HD EDW. For those who do not have HD report available, their regimen was adjusted based on their clinical parameters. The dry weight was adjusted based on their volume status during the hospitalization.

Results: Sixteen ESRD patients admitted to the hospital were included. Upon discharge, those who had outpatient dialysis reports (10 out of 16) had significant improvement of phosphorus levels, better control of the volume status, and no significant changes in hemoglobin. Three out of ten patients developed intradialytic hypotension. The average length of hospitalization was 9 days. Those who didn’t have the outpatient dialysis reports available during their hospitalization (6 out of 16) had no significant changes in phosphorus levels, post-dialysis weights, or hemoglobin. Five out of six patients developed intradialytic hypotension. The average length of stay was 10 days.

Conclusions: Patients who have dialysis rounding reports available to guide their treatment while hospitalized have better dialysis-related parameters than those who don’t.

### Table 1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>4.0 mmol/L</td>
<td>0.004</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>30.4%</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight</td>
<td>68.5 kg</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Caustic Injury After Ingestion of Naturyte®**

Guoyuan Huang, Carly Bowser, Chibuzo C. Okoye, Elena Frolova, Winston Lee. *New York City Health and Hospitals Coney Island, Brooklyn, NY.*

**Introduction:** Naturyte® is a liquid acetic acid solution—a common dialysate concentrate in the United States.

**Case Description:** A 43-year-old man with ESRD on hemodialysis (HD) and depression presented with suicidal ideation. Vital signs: BP 235/142, P 99. He was agitated, but otherwise, his exam was unremarkable. Labs showed potassium (K) of 3.7 mmol/L and bicarbonate (CO2) of 25 mmol/L. He was admitted to intensive care and scheduled for dialysis. While HD was being set up, he ingested 100 ml of the Naturyte® dialysate concentrate in attempt self-harm. He vomited immediately. After ingestion labs showed K 4.1 mmol/L, CO2 20 mmol/L and venous pH 7.4. The patient received dialysate concentrate in the United States.

**Discussion:** To our knowledge, suicide attempt by ingesting dialysate concentrate has not been reported. Naturyte® has a composition with a pH of 2.4-2.7 and various electrolytes (1) table 1. Acetic acid ingestion can cause life-threatening toxicity and multorgan failure (2). In our case ingestion of Naturyte® did not have any systemic effects; this was due to several factors. Acetic solutions often cause an immediate reaction with emesis, which limits absorption (3). Our patient was also treated with early hemodialysis. In summary, ingestion of Naturyte® can cause severe mucous membrane injury and potentially life-threatening complications.

**Composition of Naturyte®**

<table>
<thead>
<tr>
<th>Component</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic Acid</td>
<td>9.4</td>
</tr>
<tr>
<td>NaCl</td>
<td>20.6</td>
</tr>
<tr>
<td>CaCl</td>
<td>0.3</td>
</tr>
<tr>
<td>MgCl</td>
<td>0.2</td>
</tr>
<tr>
<td>pH 4.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**
Prevalence and Severity of Pruritus in Patients on Maintenance Hemodialysis
Huei Hsun Wen, Kinsuk Chauhan, Wonsuk Oh, Steven G. Coca, Girish N. Nadkarni, Lili Chan. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Chronic kidney disease associated pruritus (CKD-aP) is a common symptom in patients on in-center-hemodialysis (HD), reported in approximately 40% of patients. Recent clinical trials have identified novel agents for treatment of CKD-aP. Understanding the prevalence of urticaria pruritus and its association with other symptoms can aid in identifying patients who would most benefit from this treatment.

Methods: We surveyed patient’s ≥18 years old who had been on iHD for ≥30 days, and were receiving HD three times a week at the Mount Sinai Kidney Center. Patients completed surveys asking about the presence of absence of 21 different symptoms during the final 15 minutes of their HD treatments for 4 weeks. We performed multiple correspondence analysis (MCA) to identify associations between symptoms and group individuals with similar symptom profiles.

Results: Of the 97 HD patients who completed the study, 40 (41%) of them reported itching at least once during the study period. There were no significant differences in patient characteristics between patients who did and did not report itching (Figure 1A).

Conclusions: CKD-aP affects a large proportion of patients on HD, occurs repeatedly, and clusters with dry skin and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

Hyperkalaemia Prevalence, Recurrence, and Treatment in Haemodialysis: A Prospective Multicentre Cohort Study (PRECEDE-K Trial)
Zhaoxu Ni,1 Haijiao Jin,1 Renhua Lu,1 Li Zuo,2 Weimin Yu,1 Junsheng Wang,4 Rong Wang,4 Yuqing Ren,4 Qiongqiong Yang,5 Jie Xiao,6 Qinghong Zhang,6 Lihong Zhang,1 Xinzhou Zhang,1 Qinkai Chen,1 Chaosheng Chen,7 Guojian Shao,8 9 Shuguang Qiu,1 Hui Peng,14 Qing Zhao,19 Hongyan Shang.20 The PRECEDE-K study group ‘Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; ‘Peking University People’s Hospital, Beijing, China; ‘Shanxi Bethune Hospital, Taiyuan, China; ‘Suqian People’s Hospital of Nanjing Drum-Tower Hospital Group, Suqian, China; ‘Shandong Provincial Hospital, Jinan, China; ‘Yangquan City Hospital (Group) General Hospital, Yangquan, China; ‘Guangzhou Medical University First Affiliated Hospital, Guangzhou, China; ‘The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; ‘Taihe Hospital of Shiyian City, Shiyian, China; ‘The First Hospital of Hebei Medical University, Shijiazhuang, China; ‘Shenzhen People’s Hospital, Shenzhen, China; ‘The First Affiliated Hospital of Nanchang University, Nanchang, China; ‘The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ‘Ningbo No.2 Hospital, Ningbo, China; ‘The First Hospital of China Medical University, Shenyang, China; ‘Guangzhou First People’s Hospital, Guangzhou, China; ‘The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; ‘AstraZeneca Investment China Co Ltd, Shanghai, China.

Background: Hyperkalaemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes and is common in patients with kidney failure. However, there is no evidence on the occurrence, recurrence, and treatment of HK in patients on haemodialysis (HD) in China.

Methods: The HK Prevalence, Recurrence, and Treatment in Haemodialysis Trial (PRECEDE-K; NCT04799067) is a prospective, multicentre, observational cohort study being conducted across 18 sites in China. Approximately 600 patients with end-stage kidney disease on HD are anticipated to be enrolled and will be followed up with for 24 weeks. Patients will be in the long interdialytic interval (LIDI) at enrolment and will receive follow-up care every four weeks in LIDI for pre-dialysis and post-dialysis (at enrolment only) serum potassium measurements. To obtain pre-dialysis serum potassium levels in the short interdialytic interval (SIDI), a follow-up visit in SIDI in Week 1 will be performed. Concomitant medications, blood gas analysis, and biochemistry measurements will be obtained at enrolment and at each follow-up visit.

Results: The primary endpoint is the proportion of patients experiencing any HK (defined as serum potassium > 5.0 mmol/L) at the study enrolment or during a 24-week follow-up. The key secondary endpoint is the proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1–6 months (if applicable) during a 24-week follow-up, including enrolment assessment.

Conclusions: PRECEDE-K will generate high-quality evidence on HK recurrence, recurrence, and treatment pattern of HK in patients on HD in China, and is expected to help inform practice guidance for HK management.

Funding: Commercial Support - AstraZeneca

Dialysis in New Old Patients. Ten Years of Experience
Tatiana Tanasichuk, Daniel Kushnir, Alon Antebi, Oleg Sura, Amnon Gil, Jerom Marcuson, Yasir Sanalla, Yosef Shihada, Victoria Svistunov, Muhammad Abd Elhalim, Victor Frajewicki. Department of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.

Background: The most fast growing dialysis population during the last decades is old-age people. Mortality on dialysis patients is still high, especially among old patients. The two-year mortality rate for patients who initiate chronic dialysis over the age of 75 may exceed 50%. The risk of Acute Kidney Injury (AKI) also rises with age, while mortality risk increases dramatically in old patients with AKI. The prognosis and benefit of dialysis treatment are still unclear in very old patients. We performed a retrospective analysis of outcomes in all cases of first dialysis performed to very old patients (75 and more years old) during a 10 years period in our center.

Methods: The analysis included all ≥75 years aged patients started hemodialysis in our hospital for every indication (AKI, Acute on Chronic Renal Failure (CRF), End Stage Renal Disease (ESRD)) during the period January 1, 2009 - November 31, 2019. Patients were followed for one year from the first dialysis. The study main end point was one year all-cause mortality.

Results: In this period, 951 patients had their first hemodialysis treatment. Mean age was 82.8±5 years, 58.5% were male, 55.3% diabetics. Mean Charlson Comorbidity index was 8.3±2.2, Dementia was diagnosed in 11.4% of patients and 34.6% were nursing care dependent. Indications for dialysis were AKI in 16%, Acute on CRF in 64 % and ESRD in 20% of cases. One year mortality was 72.4%, 60% and 26.6% in AKI, Acute on CRF and ESRD respectively. Age, Nursing State, Dementia, AKI, Acute on CRF, and dialysis in a Intensive Care Unit (ICU) were associated with worse prognosis. Multivariate Cox regression models stratified by age, nursing state, AKI, Acute on CRF and ICU showed an OR of 1.3, 1.4, 3.2, 2.5, 2.0 respectively. Neither Charlson Score nor Diabetes mellitus (DM) were associated with worse prognosis. DM, in opposite, was associated with a trend of better survival although the difference was not statistically significant.
Conclusions: The outcome of very old patients started with elective maintenance dialysis was much better than in acute unscheduled hemodialysis. The baseline general condition and severity of acute illness seems to be the main prognostic factors for one year mortality. Charlson Score and Diabetes Mellitus did not influence the outcomes in this age group.

PUB103

Vaccination Rates Among Hemodialysis Patients in Nueva Ecija and Aurora Provinces

Rommel Aurora Provinces

Background: Infections is one of the most common causes of morbidity and mortality in dialysis patients. Vaccinations have been proven to give seroprotection & reduce incidences of infection. This study investigates vaccination rates among out-patient hemodialysis patients in two provinces in the Philippines.

Methods: A cross-sectional study based on hemodialysis records among patients in 12 hemodialysis centers. Vaccination records from 2018 were checked & verified in all individuals. Descriptive statistics & chi-square analysis among selective clinical characteristics were performed.

Results: A total of 550 hemodialysis patients were included in this study. 67.5% have completed their Hepatitis B vaccination. 59.1% of patients had Tetanus Toxoid 59.1% but only 46.2% had pneumococcal vaccine. Influenza vaccinations were low (2018, 11.1%; 2019, 8.4% and 2020, 8.9%). On further analysis, there are significantly more females who received Tetanus Toxoid (66.0% vs. 50.2%, p<0.01).

Conclusions: There is still a significant percentage of patients who did not receive the recommended vaccinations. Lack of access even prior to last year, financial constraints and misconceptions on vaccines may have played important roles. These have to be addressed in order to increase vaccine confidence among hemodialysis patients.

Table 1. Vaccination Rates of Hepatitis B, Pneumococcal and Tetanus Toxoid

<table>
<thead>
<tr>
<th>Age</th>
<th>Hepatitis B</th>
<th>Pneumococcal</th>
<th>Tetanus Toxoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>66.0%</td>
<td>66%</td>
<td>66.0%</td>
</tr>
<tr>
<td>40-64</td>
<td>59.1%</td>
<td>59.1%</td>
<td>59.1%</td>
</tr>
<tr>
<td>&gt;65</td>
<td>46.2%</td>
<td>46.2%</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

Continuous variables are presented as medians and categorical variables as percentages.

PUB104

Impact of Menaquinone 7 Intake on Mortality in Hemodialysis Patients

Mabel Aoun,1,2 Dania Chealala,1,2 Serge S. Finianos,1,3 Hiba Azar,1,2 'Universite Saint-Joseph, Beirut, Lebanon; 2Saint-George Hospital, Ajaltoun, Lebanon; 1Hotel Dieu de France Hospital, Beirut, Lebanon.

Background: Vitamin K deficiency was shown to be associated with vascular calcifications in hemodialysis patients. Studies evaluating the impact of vitamin K2 therapy on long-term outcomes are still scarce. This study aims to assess whether treatment with Menaquinone 7 (MK7) reduces mortality in hemodialysis patients.

Methods: This is a two-center longitudinal retrospective study that included all patients on hemodialysis during August 2016 and followed until August 2020. Some patients were treated with MK7. Data collection included vascular calcification score and dp-ucMGP at baseline, mean serum calcium, phosphate, PTH and albumin of the last year of follow-up and mortality at 1, 2, 3, 4 years. Kaplan Meier analysis was used to compare survival between the MK7 group and the control.

Results: A total of 143 patients were included. Table 1 summarizes the main differences between the two groups. Mortality was not significantly different between the two groups (Figure 1), even after adjustment to risk factors such as age, phosphate and coronary artery disease.

Conclusions: This study showed no significant difference in mortality at 4 years in hemodialysis patients treated or not by Menaquinone 7.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MK7 (n=69)</th>
<th>Control (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.5 (10.9)</td>
<td>52.6 (11.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Male</td>
<td>63.5%</td>
<td>63.5%</td>
<td>0.98</td>
</tr>
<tr>
<td>Diabetes</td>
<td>87%</td>
<td>87%</td>
<td>0.98</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>55%</td>
<td>55%</td>
<td>0.84</td>
</tr>
<tr>
<td>Mortality at 4 years</td>
<td>14%</td>
<td>15%</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Figure 1. Survival of the two groups.

PUB105

Outcome of Migrant Patients Starting Maintenance Hemodialysis in Switzerland

Thomas Fernandez,1,2 Amalie Frandsen,1,3 Pierre-Yves F. Martin,1 Patrick Saudan.1 1Hopitaux Universitaires Geneve, Geneve, Switzerland; 2Hopital de la Tour, Meyrin, Switzerland; 3Inselspital Universitasstipital Bern, Bern, Switzerland.

Background: ESRD migrants without permanent resident status is a particularly vulnerable population in regards of chronic renal replacement therapy or kidney transplantation access. Healthcare policies greatly vary between different countries which influence their clinical outcomes. Switzerland grants medical healthcare including renal care to anyone living in the country for more than 3 months.

Methods: In this report, we retrospectively analyzed the characteristics and the outcome of migrants starting dialysis at the University Hospital of Geneva (Switzerland) between January 2000 and December 2019.

Results: 775 patients started hemodialysis during this period. 38 patients (4.9%) were non-permanent residents being either asylum-seekers or undocumented. Compared to resident patients, they were significantly younger (42 and 63 years old, respectively) with less male gender (50% and 66%, respectively). The cause of ESRD was more frequently unknown with no difference for diabetes prevalence. Their modified Charlson
comorbidity index was overall lower. Emergency hemodialysis initiation was more frequent and mean TFPR at dialysis start was significantly lower (5 vs 7 ml/min/1.73m2). Most of the migrant patients eventually obtained a stable resident status (24/38, 63 %). Seven were sent back to their home country (7/38, 18 %) and 3 were lost of follow-up (3/38, 8%). Among the 28 migrant patients who stayed in Switzerland, 6 patients died during the study period and 17 (61%) obtained a kidney transplantation. To account for their characteristic differences, propensity score matching was performed. Time to transplantation after dialysis initiation was significantly delayed for migrants with a median time to transplantation of 60 (43-99) and 25 (12-49) months for eligible migrants and matched residents, respectively. Survival censored for kidney transplantation was overall significantly much higher in migrants compared to resident patients with a 5-year survival rate of 85% and 55%, respectively. When censored for kidney transplantation, survival remained better among migrants compared to matched residents (85% and 65% at 5 years, respectively).

Conclusions: In conclusion, ESRD clinical outcomes are excellent when standard care is provided. Aside the ethical issue, previous data from the US suggested that it is economically sustainable.

PUB106

The Cost of the Quanta SC+ Hemodialysis System for Sustained Low-Efficiency Dialysis in the Intensive Care Unit

Thomas W. Ferguson,1 Paul Komenda,2,3 Christos Argyropoulos,3 Seven Oaks General Hospital, Winnipeg, MB, Canada; 2Quanta Dialysis Technologies Ltd, Alceter, United Kingdom; 3University of New Mexico School of Medicine, Albuquerque, NM.

Background: Over 20% of patients in the intensive care unit (ICU) who receive hemodialysis are not ready for transfer to a chronic hemodialysis facility. There are several modalities available to provide dialysis in the ICU, including conventional hemodialysis, continuous renal replacement therapy (CRRT) and sustained low-efficiency dialysis (SLED). Recent meta-analyses have found that there is no definitive advantage of either of these modalities with respect to patient outcomes; however, they are associated with different cost and resource requirements. The SC+ Hemodialysis System is a commercially available, portable hemodialysis system that can be operated with minimal training by ICU nurses.

Methods: We described the incremental costs of CRRT, regular 4-hour conventional dialysis provided by specialized hemodialysis nurses, and SLED with the SC+ Hemodialysis System in the ICU. The analysis was performed from the perspective of the US health payer with results presented in 2020 US dollars. We considered costs with respect to the dialysis console, dialysis-related supplies (cartridges, tubing, dialyzers, dialysate, bags, and saline), and nursing-related human resources modeled from a large US based hemodialysis program.

Results: The cost of CRRT assumed that ICU nursing staff would provide the therapy, with consumables costs ranging between $320 and $380 per ICU-day. Dialysis provided with conventional 4-hour therapy in the HD unit ranged between $205 and $245 per day including both incremental nursing and renal technician expenses and consumables. Dialysis provided with the SC+ as 8-hour SLED treatments was estimated to cost between $59 and $85 for consumables and operated by the ICU nursing staff.

Conclusions: SLED treatment with the Quanta SC+ operated by ICU nurses offers significant cost advantages over CRRT and conventional HD treatments with no demonstrable disadvantage to patient outcomes.

Funding: Commercial Support - Quanta Dialysis Technologies

PUB107

Incident Dialysis Patients in Latin America (LA): An Unpaid Debt

Adrian M. Guinsburg,1 Maria Ines Diaz Bessone,1 Juan Carlos Berbessi,1 Alejandro Kohn Tuli,4 Ana Beatriz L. Barra,2 Eduardo A. Machuca,3 Jesus E. Munoz,4 Leonor E. Briones,4 Maria L. Quintanilla,5 Maria M. Resk,6 Gabriela R. Cannatelli,1 Beatriz P. Schrittmeyer,1 Jorge M. Caseiro,7 Fresenius Medical Care LatAm, Fresenius Medical Care LatinAmerica, Rio de Janeiro, Brazil; 7Fresenius Medical Care Chile SA, Santiago, Chile; 8Fresenius Medical Care Ecuador, Quito, Ecuador; 9Fresenius Medical Care Peru, Lima, Peru; 10Fresenius Medical Care Argentina SA, Buenos Aires, Argentina; 11Fresenius Medical Care Colombia, Bogota, Colombia; 12Fresenius Medical Care Caricam, Quito, Ecuador; 13Fresenius Medical Care Peru, Lima, Peru; 14Fresenius Medical Care Brazil, Rio de Janeiro, Brazil; 15Fresenius Medical Care Brazil, Rio de Janeiro, Brazil; 16Fresenius Medical Care Colombia, Bogota, Colombia; 17Fresenius Medical Care Caricam, Panama, Panama.

Background: Predialysis care in LA is conditioned by uneven accessibility to adequate treatment and odds healthcare systems. Timely initiation, vascular access (VA) creation and anemia and bone disease management are still barriers to overcome. The aim of this study was to compare incident (INC) and prevalent (PRV) dialysis patients outcomes from Fresenius Medical Care LA (FME LA) and possible correlations with survival.

Methods: Patients from FME LA (Argentina, Brazil, Chile, Colombia, Ecuador, Peru) from 18 years and older, incident between Jan 1 and Dec 31, 2020, were included. INC were defined with <90 days since first treatment in life and PRV >90 days. INC accounted during first treatment. Dialysis was provided by specialized hemodialysis nurses, and SLED with the SC+ operated by ICU nurses. The Diality Hemodialysis Machine will provide tight control to provide dialysis in the ICU, including conventional hemodialysis, continuous renal replacement therapy (CRRT) and sustained low-efficiency dialysis (SLED).

Results: Table 1 shows the characteristics of the study population. 51% of patients were female, 79% of patients were white, and 79% were Hispanic. Their median age was 65 years (IQR: 54-76). The most common co-morbidities were diabetes, hypertension, and heart disease. The median time to transplantation was 60 (43-99) and 25 (12-49) months for eligible migrants and matched residents, respectively. Survival censored for kidney transplantation was overall significantly much higher in migrants compared to resident patients with a 5-year survival rate of 85% and 55%, respectively. When censored for kidney transplantation, survival remained better among migrants compared to matched residents (85% and 65% at 5 years, respectively).

Conclusions: In conclusion, ESRD clinical outcomes are excellent when standard care is provided. Aside the ethical issue, previous data from the US suggested that it is economically sustainable.

Table 1: Incident / Prevalent patients characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident (INC)</th>
<th>Prevalent (PRV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (54-76)</td>
<td>65 (55-75)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>51%</td>
<td>49%</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>79% Hispanic</td>
<td>79% Hispanic</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>47%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>32%</td>
<td>32%</td>
</tr>
</tbody>
</table>

PUB108

Ultrafiltration Accuracy in a Modified Batch Dialysis System

Clayton Poppe, Nicholas Hyun, Sean C. Nash, Melany Yeung, Osman Khawar, Diality Inc, Irvine, CA.

Background: Ultrafiltration accuracy is an important way of improving mortality and morbidity on dialysis. The Diality Hemodialysis Machine will provide tight control of ultrafiltration during treatment. Specific Aims: To assess ultrafiltration accuracy during simulated dialysis utilizing a novel modified batch process. In this setup, ultrafiltration was conducted by alternating collection into two-liter reservoirs that contain dialysate and ultrafiltrate.

Methods: Two simulated dialysis sessions were conducted utilizing blood flows rates of 300 ml/min, dialysate flows of 300 ml/min and ultrafiltration flows of 7500 ml/hr. (Table 1) Dialysis and ultrafiltration occur off of a two-liter batch of dialysate. Once two liters of dialysate has been circulated through the dialyzer, the collected ultrafiltrate and spent dialysate are discarded and dialysis switches to a separate two-liter reservoir of dialysate while the first reservoir is drained and filled with fresh dialysate.

Results: The results are provided in Table 1. The average ultrafiltration accuracy was measured by comparing the machine-calculated ultrafiltration volume with the weight of the simulated patient. The mean error represents the average difference between machine and patient during the simulated treatments, while the total error represents the total error after the simulated run was completed.

Conclusions: The initial experiments using a modified batch system show promising ultrafiltration accuracy. Future tests will demonstrate accuracy over a larger range of flowsrates, volumes and times.

Funding: Commercial Support - Diality Inc

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Incident (INC)</th>
<th>Prevalent (PRV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Error</td>
<td>1.86%</td>
<td>2.34%</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.86%</td>
<td>2.34%</td>
</tr>
</tbody>
</table>

PUB109

Recruitment Experience for a Year-Long Prospective Observational Study Using a Commercially Available Wearable Device

Magzie Han,1 Xia Tao,1 Ohnmar Thwin,1 Lemuver Rivera Fuentes,1 Priscila Preciado,1 Leticia M. Tapia Silva,1 Mohamad I. Hakimi,1 Jochen G. Raimann,1 Peter Kotanko,1,2 Renal Research Institute, New York, NY; 1Columbia School of Medicine at Mount Sinai, New York, NY.

Background: Wearable activity trackers can allow healthcare providers to access patients’ health parameters remotely. These commercially available devices may provide valuable insights at low cost. Research of the use and acceptance of this technology is important to scale the use of trackers and integrate them into clinical care. We aim to share our experience of recruiting hemodialysis (HD) patients to a research study using a wearable activity tracker.

Methods: Patients were recruited in 4 dialysis clinics in Manhattan, NYC. Patients who received their attending nephrologist’s approval to participate in the study were approached for recruitment. Patients ≥18 years on maintenance HD, able to walk, owning smartphone, tablet or PC were included in the study. Patients were observed for up to 1 year and were asked to wear a Fitbit Charge 2™. Questionnaires were administered to assess physical and emotional well-being. Subjects who inconsistently synced their Fitbits were withdrawn. We enrolled continuously from May 2018 to November 2019.

Results: Only a third of patients who were approached consented to participate in our study. 76% of patients who were eligible did not participate in the clinical study. Details of the recruitment and enrollment process are shown in the flowchart in Figure 1.
Conclusions: With most eligible patients choosing to not participate, the value of patients’ contributions to research needs to be emphasized. We encourage healthcare providers to take the time to educate patients on the importance of clinical research.

Funding: Commercial Support - Fresenius Medical Care
Vitamin D Independently Related to Right Ventricular Dysfunction in ESRD Patients on Maintenance Hemodialysis

Firoozeh Farahmand, Saint Louis University, Saint Louis, MO.

Background: Right ventricular (RV) dysfunction is a major cause of death in patients undergoing maintenance hemodialysis (HD) and a major determinant of mortality in pulmonary hypertension that is common in HD patients. There is tremendous amount of data on left ventricular function in HD patients, but data on right ventricular function and its mechanisms in HD patients are scarce. It has been suggested that vitamin D could be involved in the development or progression of heart failure by modulating oxidative stress. We investigated changes in RV function in HD patient and its correlation with vitamin D level.

Methods: In a university affiliated dialysis center, a retrospective cohort of ESRD patients treated with HD for at least 1 month followed in a dialysis unit. Patients without vitamin D assessment, prior myocardial infarctions, heart failure, or prevalent valvular disease were excluded. Subject characteristics were recorded, including age, gender and race. Echocardiography including tissue Doppler imaging (TDI) of the RV was evaluated. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Results: A total of 77 HD patients were included in the study. The mean age of the patients was 53.7±4.7 years. The mean dialysis vintage was 27±14 months. The mean ejection fraction was 45±7%. The prevalence of PHT was 53%. 59% of patients had RV dysfunction on echo. 72% of patients with RV dysfunction had a 24hOHDJ level <70g/ml (p<0.05). 30% of patients had RV dysfunction on echo. The prevalence of PHT was 53%. 59% of patients with PH were female that was statistically (p<0.05). 30% of patients had RV dysfunction on echo. 72% of patients with RV dysfunction had a 24hOHDJ level <70g/ml (p<0.05). We also demonstrated a higher prevalence of RV dysfunction among ESRD patients under maintenance HD and it is strong association with suboptimal vitamin D. Further investigations are required to evaluate the beneficial effects of cholecalciferol in ESRD patients with RV dysfunction.

Conclusions: Our study demonstrates that vitamin D level is independently related to RV dysfunction in patients on maintenance HD. Further investigations are required to evaluate the beneficial effects of cholecalciferol in ESRD patients with RV dysfunction.

Mortality and Associated Factors in Patients Under Hemodialysis in a Latin American Tertiary Center

Annette G. García Delgado, Jennifer P. Khoury, Nicole De Los Santos, Anthony D. Núñez-Díaz-Batlle, Pontificia Universidad Católica Madre y Maestra Facultad de Ciencias de la Salud, Santiago De Los Caballeros, Dominican Republic; Hospital Metropolitano de Santiago, Santiago De Los Caballeros, Dominican Republic.

Background: Risk factors are associated with the prognostic and early diagnosis of chronic renal disease. We evaluated modifiable and non-modifiable factors related to mortality in patients who receive hemodialysis therapy.

Methods: Retrospective cohort study. 47 patients were included. The mean age was 56.29, 71.13% were female, and 55.6% had more than two comorbidities. Diabetes and hypertension were the most common causes of chronic renal disease. Male participants were more likely to die than females. The Charlson index was higher in patients with RV dysfunction than those who did not die (5.13±7.3). Patients with lower hemoglobin and albumin levels were more likely to die. Also, calcium levels [9.05 (8.5–9.4)] were higher in deceased patients. 69.23% of patients who died used central venous catheter access lines.

Conclusions: The use of central venous catheters is an important risk of mortality to patients who receive hemodialysis therapy. Other factors associated with mortality in these patients are an elevated Charlson index, low hemoglobin, albumin, and high calcium levels. These results show the importance of an early assessment of the patient and the factors mentioned above.

Atraumatic Splenic Rupture in a Patient on Apixaban and Clopidogrel


Introduction: Atraumatic splenic rupture (ASR) has an estimated overall mortality rate of 2.8% and a 2.4% of cases requiring surgery. Our patient was an 82-year-old female who was started on Celtrafine and Flagyl for the concern of spontaneous bacterial peritonitis in addition to pantoprazole drip, Octreotide drip, Norepinephrine, and vasopressin for hepatoportal syndrome. Due to worsening kidney function hemodialysis was initiated on day 18 of hospital admission using the Fresenius Optiflux 180 dialyzer with a synthetic polymer (electron-beam sterilized) membrane. The patient tolerated the first hemodialysis session without complications. However, on the next day, his platelet count decreased from 120,000 to 25,000. Workup was negative for other causes of thrombocytopenia. On the fourth hemodialysis session, the dialyzer was switched from the F180N to Purema-Polyethersulfone dialyzer (gamma sterilized), after which the patient’s platelet levels began to recover without any regression.

Discussion: Thrombocytopenia is a well-known complication of hemodialysis treatment, which results in platelet adhesion, aggregation, and activation. A post-dialysis platelet count decrease of more than 15% compared with predialysis values could identify dialysis-related thrombocytopenia. Verbeelen et al. showed that cellulose acetate dialysis membranes could cause transient thrombocytopenia and platelet activation. In our patient’s case, electron beam sterilization was used initially with the Optiflux 180 Polysulfone dialyzer, and the thrombocytopenia resolved when he was switched to the Purema-Polyethersulfone dialyzer that was gamma sterilized. This case of hemodialysis-associated thrombocytopenia in a case of HD patient demonstrates that polysulfone dialysis membranes can variably affect platelet levels, despite previous evidence indicating that polysulfone membranes do not affect platelet counts.

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her INR increased to 1.62. An urgent abdominal CT scan revealed splenic rupture and significant hemoperitoneum (Figure 1). An emergent exploratory laparotomy revealed splenic rupture and she underwent splenectomy. On pathologic examination, the spleen measured 12 x 6.5 x 1.9 cm with evidence of an organized splenic hemangioma.

**Discussion:** DOACs significantly reduce mortality from embolic complications in patients with atrial fibrillation but increase the risk of gastrointestinal bleeding. Additionally, patients on a DOAC with an add-on antiplatelet agent may experience a delayed coagulation factor and increase the risk of hemorrhage. Furthermore, pharmacokinetic studies suggest that use of apixaban, even at recommended doses, may lead to supratherapeutic inhibition of factor Xa in patients with ESRD. Therefore, ASR should be suspected in any patient maintained on anticoagulation who presents with abdominal pain and shock, especially those who are taking both a DOAC and antiplatelet therapy. Bedside ultrasound showing free peritoneal fluid can aid in early diagnosis of these patients.

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**Case Description:** A 56-year-old female with ESKD presented to the outpatient PD clinic with 4 months of outflow and inflow failure. Four months later, the patient presented with outflow failure and bulge at the catheter insertion site. Abdominal radiograph showed appropriate positioning of the catheter tip in the right lower quadrant. Laparoscopic surgery showed an incisional hernia at the previous peritoneal entrance site and no catheter in the peritoneal cavity. Incision of the bulge revealed a protrusion of peritoneum. The patient refused surgery and was discharged home. The patient was complicated by pancytopenia, CMV viremia, acute decompensated heart failure and severe symptomatic gastroparesis raising concerns on whether she can continue PD. At baseline. With a coordinated effort between surgery, cardiology and nephrology, she had NYHA Class IIIB symptoms, CardioMEMS implantation a year prior and being evaluated for combined heart-kidney transplant. She also had symptomatic orthostatic hypotension for combined heart-kidney transplant. She also had symptomatic orthostatic hypotension. In this case, she presented with PD catheter insertion site swelling. She underwent revision of the catheter where a pericatheter hernia at the peritoneal insertion site was found. The sac was sewn to incorporate the cuff, the old catheter was cut and tunneled to a new site. 6 months later, the patient presented with outflow failure and bulge at the catheter insertion site. Abdominal radiograph showed appropriate positioning of the catheter tip in the right lower quadrant. Laparoscopic surgery showed an incisional hernia at the previous peritoneal entrance site and no catheter in the peritoneal cavity. Incision of the bulge revealed a protrusion of peritoneum. The patient refused surgery and was discharged home. The patient was complicated by pancytopenia, CMV viremia, acute decompensated heart failure and severe symptomatic gastroparesis raising concerns on whether she can continue PD. She was successfully discharged home on PD and home PD regimen adjusted to attain a reasonable SLED.
goal PA diastolic pressure of 18-20 mm Hg (Figure 1). Rehospitalizations were prevented and she eventually received a combined heart-kidney transplant 3 months later.

Discussion: Assessment of UF needs in dialysis patients with HF is fraught with multiple limitations leading to frequent rehospitalizations. In our patient, PA diastolic pressure readings from CARDiOMEMs were used as a guide in assessing UF needs and adjusting PD regimen. Our case illustrates that a coordinated multidisciplinary approach can provide patient-centered care at home and improve outcomes.

PUB122
Development of a Registry for Peritoneal Dialysis at Yokohama City University and Affiliated Hospitals (Yokohama Bay-Shonan PD Registry)
Tomohiko Kanaoka, Sho Kinguchi, Kengo Azushima, Hiromichi Wakui, Kouichi Tamura. Yokohama City University Graduate School of Medicine, Department of Medical Science and Cardiorenal Medicine, Yokohama, Japan.

Background: Patient registry has become increasingly important as a strategy to promote clinical research and to improve the patient care. Yokohama City University Hospital is one of the leading hospitals in Kanagawa Prefecture, a representative and well-known urban area in Japan.

Methods: We started to construct a registry of peritoneal dialysis (PD) at Yokohama City University Hospital and 15 affiliated hospitals (Yokohama Bay-Shonan PD Registry) from the beginning of 2020. The categories of Yokohama Bay-Shonan PD Registry include an information including the age, sex, duration of PD, method of PD (continuous ambulatory PD, intermittent PD, or continuous cyclic PD), cause of end stage of kidney disease, prescription of renin-angiotensin system inhibitors (+/−), past history of heart disease (+/−), results of peritoneal function test, onset of new heart disease (+/−), onset of PD-related infection (+/−), and combination of hemodialysis (+/−).

Results: We collect data from each facility once a year. Only data of Yokohama City University Hospital were available for analysis this time, and total of 28 patients were registered at Yokohama City University Hospital. Mean age was 66.7 years old. Eleven patients were affected with PD-related infection, and 5 patients discontinued PD (1 death, 1 pancreas cancer, and 1 PD-related infection).

Conclusions: We continue to collect data from each affiliated hospital and will expand the information recorded in the Yokohama Bay-Shonan PD Registry to find the persistence rate of PD and frequency of cardiovascular events for further analysis.

PUB123
Unusual Pathogen Causing Peritonitis in a Peritoneal Dialysis (PD) Patient
Rula A. Abdulrahman. Stony Brook University, Stony Brook, NY.

Introduction: Pantoaea species causes infection in humans and are pathogenic to plants. Pantoaea agglomerans are mostly isolated from human and was reported to cause peritonitis. We are describing a case of peritonitis in a PD patient, caused by Pantoaea Calida (PC) and Pantoaea Gaviinae (PG). There are few case reports about it causing bacteremia, meningitis infection in human but not peritonitis.

Case Description: 44 years old man on continuous cycling PD, has history of cardiomyopathy, was found to have cloudy effluent and was complaining of abdominal pain, nausea and diarrhea. Vitals signs: temperature 38 ℃, BP 126/80, PR 91. on exam: cardiomyopathy, was found to have cloudy effluent and was complaining of abdominal tenderness. Effluent fluid analysis cell counts of 3408/μL, with 80% polymorph neutrophils. patient was prescribed intravenous antibiotics vancomycin and cefepime, then started on continuous cefepime intraperitoneal the next day, while effluent culture was pending. On day 5 patient was feeling better and the cell count dropped to 1996/μL, so was discharged home. Cefepime was continued intraperitoneally. 2 days after discharge, effluent was noted to be cloudy again and the cell count was 2948/μL. At this time decision was made to remove PD catheter for persistent peritonitis. Effluent was consistent with PC & PG, susceptible to cefepime. Fungal culture remain negative. PD catheter was removed & Patient was started on hemodialysis. patient was treated with ceftazidime for 2 weeks. infection was treated, patient chose to remain on hemodialysis.

Discussion: Peritonitis is a common and serious complication of PD. It is the major cause of death in around 16% of PD patients.it is reported that Pantoaea agglomerans can cause peritonitis. Our patient had peritonitis caused by PC, PG which is a very rare finding. Despite treatment with appropriate antibiotic the symptoms persist and eventually PD catheter was removed, the patient was started on hemodialysis. Pantoaea species have been isolated from soil, water, plant, seeds, fruits, and human body fluids. PG, and PC were isolated from infant formula. PC was isolated from dialysate of PD patients and from urine, although pathogenicity remain unknown. In our case the patient had severe peritonitis caused by Pantoaea species, the way of transmission is unclear. We recommend further research and examining the dialysate fluid in certain population, aiming that such an infection can be prevented in future.

PUB124
The Effects of Location of Peritoneal Dialysis Training, In-Home vs. In-Center, on Peritoneal Dialysis Patients
Rajeev Chauhan,1 Mallicka Chauhan,2 Renal Associates LLC., Columbus, GA; New York Institute of Technology, Old Westbury, NY.

Background: The objective of this study is to investigate the relationship between peritonitis rates and whether peritoneal dialysis (PD) was taught in-center (n=104) or in-home (n=16) for 120 patients in a single center located in Southern Georgia. Previous studies have assessed the link between peritonitis rates and demographic factors among PD patients. However, there is very limited research that examines the effects of peritoneal dialysis training location on a patient’s chance of developing peritonitis.

Methods: This study is a retrospective analysis for data accumulated over a period of seven years. Subjects were categorized into two groups: one group’s dialysis administrator received peritoneal dialysis training in their homes and the other group’s dialysis administrator was trained in-center. The data collected includes gender, age, peritonitis occurrence, presence of family support to patient, and severity of comorbidities.

The initial analysis was conducted by using a Fischer’s test and Welch’s t-test. Further investigation was done through a Cox hazards model to compare the influence of in-home and in-center training on peritonitis occurrence over time during PD.

Results: A hazard ratio (HR=0.377) was utilized to compare the home trained group to the center trained group. The HR indicates that at any time during PD, patients who were home-trained had a 62.3% lower risk of peritonitis. The confidence interval includes one. Therefore, this result is not significant, and this finding is further verified by its p-value being over 0.05. Additionally, significant difference between peritonitis rate and location of training (P=0.4352) could not be established and all models used to analyze each variable resulted in insufficient p-values and binary squared values.

Conclusions: Considering the use of unbalanced sample sizes and limited data, the results can be deemed misrepresentative of the general peritoneal dialysis patient population, this study finds that location of training, in-home versus in-center, may not be an accurate gauge of peritonitis risk in certain populations.

PUB125
Curious Rash
Parth Worah, Jingyin Yan, Sehrish Ali. Baylor College of Medicine, Houston, TX.

Introduction: Peritoneal dialysis (PD) involves infusing a solution into the peritoneal cavity via a catheter. PD provides removal of solute/fluids by using the peritoneal membrane as an exchange surface. Primary PD solutions are glucose containing. Glucose is not an ideal osmotic agent as it’s easily absorbed; thereby attenuating the osmotic gradient driving ultrafiltration (UF). Icodextrin (ID) is an alternative to hyperosmolar glucose containing solutions. ID is an iso-osmolar solution consisting of a mixture of high molecular weight water-soluble polymers of glucose, isolated by the fractionation of hydrolyzed cornstarch. It’s added when more UF is indicated and/or when patients are at an increased risk of hyperglycemia. Icodextrin is generally well-tolerated; however, there have been reports documenting exfoliative rash from it. Our case describes biopsy proven spongiotic dermatitis on a patient who recently had ID added to her PD prescription.
Case Description: A 38-year-old female with past medical history of DM, HTN, and ESKD on PD for 1 year, presented with diffuse dry skin, pruritic rash and excoriations. This occurred 4 days after changing her PD solution to ID. It worsened despite a 3 day course of steroids. Physical exam notable for diffuse subcutaneous desquamation and excoriation. Labs showed mild leukocytosis with a neutrophil predominance. Upon removal of ID from the PD prescription, her symptoms improved and a slow resolution of the skin rash occurred. Biopsy showed spongiotic dermatitis, consistent with eczematous/contact dermatitis.

Discussion: ID provides a continuous and longer osmotic gradient because it is absorbed through the peritoneal cavity slower than standard PD solutions. Therefore, ID is used to increase UF. A few case reports and studies documented rare hypersensitivity reactions and exfoliative rashes to ID in dialysis patients. The exact pathophysiologic mechanism is not fully understood, ID is slowly absorbed via the lymphatic system from the peritoneal cavity, and is rapidly hydrolyzed by amylase in maltose, which may cause pruritus. Hypersensitivity reactions may be caused by immune complex formation on the skin. Our case shows a case of spongiotic dermatitis caused by edema and exocytosis of lymphocytes. ID induced skin rashes typically resolves with discontinuation of ID, yet clinicians should remain attentive and consider these potential side effects in patients that develop skin rashes after being initiated on ID solution.

A CT peritoneogram showed the catheter in good position in the pelvis overlying the bladder. Laparoscopic exploration was pursued. This showed no significant adhesions or omentum. The catheter was manipulated away from bowel and secured to the abdominal wall. This resolved the patient’s pain.

Discussion: Pain with dialysate drain is often due to catheter obstruction by omentum, bowel, bladder or the peritoneal membrane. Treatment of constipation or use of tidal fill volumes are initial strategies used to address this. When noninvasive methods fail to correct the issue, imaging can help identify tip migration or any adhesions. In the presented cases, we highlight how laparoscopy can be an important tool to salvage a PD catheter, and correct any mechanical obstacles complicating PD therapy.

**Figure 1.** (A) X-Ray from Case 1, (B) CT from Case 2

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**PUB126**

Novel Combined Test for Osmotic Conductance to Glucose and Small Solute Diffusion Capacity in Peritoneal Dialysis


Background: Peritoneal membrane small solute diffusion capacities and osmotic conductance to glucose (OCG) are key determinants of peritoneal dialysis treatment efficiency and patient outcomes. However, current peritoneal function tests for measuring these parameters are cumbersome, inaccurate, and time-consuming. Recently, we developed an easy method to determine OCG on the basis of a single 1-h 4.25% glucose dwell (Fig. 1A). Here, we retrospectively assess the ability of the single dwell method to accurately determine also the diffusion capacity (PS) for creatinine.

Methods: Using a recently developed isocratic method, creatinine PS values were firstly determined on the basis of a single 1-h 4.25% dwell, and then validated against a reference Three-pore model creatinine PS in a Bland-Altman analysis (n=28). Also, a simple equation was developed to convert between PS assessed using 1-hour dwells of 1.5% and 4.25% glucose fluid.

Results: Isocratic PS estimations based on the single 1-h 4.25% dwell correlated closely with the reference method (Fig. 1B) (r=0.98), and had a mean difference of 0.6 ± 1.0 (1.96 SD) mL/min (Fig. 1C). The 1.5% glucose data showed higher variation, having a mean difference of -0.6 ± 3.9 mL/min and r=0.81 (P<0.001).

Conclusions: The combined single dwell peritoneal function test shows promising estimation accuracy for both creatinine PS and OCG. The present retrospective findings need to be confirmed in a prospective clinical study.
Abdominal Cocoon Syndrome in Peritoneal Dialysis

J. G. van Baardwijk, Carlos Kuria, Joe N. Austin. Christ Hospital, Cincinnati, OH.

Introduction: Abdominal cocoon syndrome, also known as sclerosing encapsulating peritonitis (SEP), is a rare form of small bowel obstruction (SBO) resulting from peritoneal inflammation inducing formation of a fibrocollagenous membrane. Secondary (non idiopathic) SEP is seen in patients on peritoneal dialysis, peritonitis, previous abdominal surgery, sarcoidosis, or tuberculosis. We present an interesting case of secondary SEP.

Case Description: A 54-year-old African American male with history of end-stage renal disease on hemodialysis (HD), sclerosing encapsulating peritonitis, recurrent SBO presented with weakness, failure to thrive and fecal drainage through his incision site. Because of his weakness, he had missed two HD sessions. Two and half weeks prior to presentation he was admitted for SBO and underwent ex-lap with lysis of adhesions, administration of antibiotics and permanent cessation of oral intake. Abdominal wound cultures grew enterocutaneous fistula and extensive coarse intraperitoneal calcifications consistent with SEP abscess. He had been on peritoneal dialysis (PD) for about 20 years which was converted to HD due to interval development of intraperitoneal calcification consistent with SEP. He had been on peritoneal dialysis (PD) for about 20 years which was converted to HD due to interval development of intraperitoneal calcification consistent with SEP. He had been on peritoneal dialysis (PD) for about 20 years which was converted to HD due to interval development of intraperitoneal calcification consistent with SEP.

Results: 23 adult patients on peritoneal dialysis were reviewed. Baseline characteristics included 12 females age 25-76, 11 males 32-87; 9 diabetics; 3 on CAPD, 20 on CCPD. Peritoneal membrane transport type included 1 low, 9 low average, 11 high average, and 2 high. PD prescriptions accounted for 37-217 grams of carbohydrates and 128-868 calories based on individual prescriptions (% dialysate used, transport properties, modality).

Conclusions: Quantifying the calories and grams of carbohydrates from the dialysate in peritoneal dialysis is easily accessible through PD ADEQUEST software and is extremely valuable to improve the care of diabetics with ESRD. This information can help optimize blood sugars and improve eligibility for transplant. Estimating caloric absorption on peritoneal dialysis is important for patients needing nutrition support to avoid over/underfeeding and should be considered in patients who struggle with obesity.

A Central Venous Catheter That Cannot Be Dislodged Easily by a Confused Patient

Shuqin Mei, Shanghai Changzheng Hospital, Shanghai, China.

Introduction: The optional type of permanent access for hemodialysis among the elder is controversial. Reliable vascular access which can provide adequate blood flow is a prerequisite for hemodialysis. Exhausted vascularule, patient comorbidities, and life expectancy should be taken into consideration for whether it is worth to place an arteriovenous fistula (AVF)/arteriovenous graft (AVG). So the tunneled central venous hemodialysis catheter are both preferred choices for end-stage renal disease patients who have an urgent need for hemodialysis. But sometimes patients dislodged or pulled out central venous catheters by mistake or confused.

Case Description: A 75-year-old hemodialysis man with a history of multiple arteriovenous fistula operations was admitted to our clinic for the poor blood flow of 150ml/min. Although the AVF was historically known to be the ideal option for vascular access, the aging old man had no chance because of the poor vessel quality on both arms, and the tunneled hemodialysis catheter was optioned to be chosen. In view of the cerebral infarction induced intelligence obstacles of the patient, atypical tunnel of the catheter should be considered in case of the catheter pulled out by the patient unconscious. During the procedure without fluoroscopy, the guidewire entered the vessel smoothly after successful puncture into the right external jugular vein with the left lateral position of the patient. The exit of the tunnel was 5cm right to the middle of the spine at the level of the third thoracic which was out of reach of the patient and a cuffed hemodialysis catheter was eventually inserted through the peel-away sheath, and finally the catheter entered the vessel with satisfactory venous blood return. Hemodialysis was initiated with blood flow 200ml/min with no complication.

Discussion: To find a solution for confused or uncooperative patients, we conducted a different method. On the basis of our experience, we recommend clinicians consider using these techniques when placing a central venous catheter in a patient who is confused or uncooperative to prevent the patient from dislodging it. Although the back exit at the level of the third thoracic is better to avoid dislodging the central venous catheter comparing with the normal exit, it may uncomfortable when the patient lying on bed or receiving hemodialysis treatment. Anyway, the best method is the right and suitable for the patient.

Hemodialysis Catheters: the Good, the Bad and the Ugly

Jafar Alsaid, Ochsner Medical Center - New Orleans, New Orleans, LA.

Background: Over the past decades with all the efforts spent for fistula first, hemodialysis catheters are still used in more than 80% of patients for hemodialysis initiation. Moreover, up to 18 months after starting dialysis around 20% of the patient still have catheters as the main vascular access. Catheters are a vital component of our ESRD renal replacement care, and we need to learn more about them. This review covers all the evidence based data on HD catheters. “Knowing your enemy would give a leading step in winning the battle” Art of War.
Vascular Access: A Screening Medical Device to Identify Patients at Risk for Access Dysfunction and Thrombectomy

Suha A. Alkousay,1,2 Xueqin J. Zhou,3 Hong Y. Cao,4,5 Xian L. Nava,1,2
1Division of Nephrology, California Pacific Medical Center, San Francisco, CA; 2Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI; 3Midwestern University - Dripping Springs, Arizona, AZ; 4First Affiliated Hospital of Nanjing Medical University, Nanjing, China; 5Vascular Access & Consulting, Lafayette, IN.

Introduction: USRC Oakbrook has 13 dialysis stations for patients with end-stage kidney disease. The Medical Director wanted to improve patient outcomes by implementing vascular access management. Vasc-Alert, an FDA-approved medical device, was used to screen for vascular access stenosis and provided reports with historical results upon initial staff training. Vasc-Alert was effective in identifying patients at risk for access dysfunction, which if left undetected can increase the risk for thrombosis.

Case Description: Initially, Vasc-Alert identified 9 patients on alert. 6 were deemed high risk. 4 patients were successfully referred for an angioplasty, but 2 patients thrombosed before referral. The remaining 3 alert patients were considered low risk. This report discusses 2 specific patients Vasc-Alert identified and proved intervention was needed. WA presented in March 2019 with no significant problems and met Kt/V. The patient was routinely on alert and later had longer post-bloodling time and plateaunab data. Referred in April 2021 after Vasc-Alert training. The Kt/V and post-bloodling time significantly dropped. The patient has had no alerts and has been achieving adequacy. BP presented to USRC in January 2019 and had an angioplasty with minimal problems. Prior to thrombectomy in March 2021, BP was consistently on alert with no other clinical indicators of dysfunction. Clinical training for Vasc-Alert occurred two days prior to her clotting. There was insufficient lead time to refer based on Vasc-Alert data, but it is sufficient to deduce that Vasc-Alert successfully predicted future clotting.

Discussion: While USRC had an active vascular access management program, these 6 patients were not previously identified. The introduction of the Vasc-Alert surveillance helped focus on the patients at the greatest risk. While the 2019 KDQCC guideline for vascular access discounted the use of surveillance devices from the prior 2006 guidelines, this case study indicates that surveillance devices can still be useful in helping busy staff focus on patients at high risk of complications. Vasc-Alert has successfully alleviated future procedural issues and has the potential to improve diagnosis and treatment plans for patients with access dysfunction.

Vascular Access for Hemodialysis Patients: A Retrospective Observational Study

Xueqin J. Zhou, Hong Ye, Wenjing Zhou, Yang Zhou, Junwei Yang. Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: To demonstrate the clinical efficacy and safety of ambulatory surgery for vascular access of hemodialysis patients.

Methods: A total of 1845 hemodialysis patients receiving ambulatory surgery for vascular access from September 2017 through December 2020 were enrolled. The clinical characteristics, surgery procedures, safety, efficacy and cost of the operations were analyzed.

Results: The mean age was 57.1 years, 53.4% were male, and mean dialysis vintage was 61.9 months. The percentages of the existing vascular accesses of arteriovenous fistula (AVF), arteriovenous graft (AVG), tunnel-cuffed catheter (TCC) and non-cuffed catheter were 58.4%, 30.9%, 3.3% and 3.9%, respectively. The operation methods of ambulatory surgery was interventional surgery (82.3%), hybrid surgery (11.4%), TCC (4.1%) and digital subtraction angioplasty (1.3%). All of the surgery was successfully completed, and the primary patency rate was 100% at 30 days after the surgery. The average operation time was 68.3±10.6 minutes. The average duration of hospitalization was 17.7±6.3 hours. The average total cost of each hospitalization was 9121.3±2818.3 RMB including the operation fee of 2211.7±843.2 RMB and disposable medical material cost of 4587.6±2073.2 RMB.

Conclusions: Ambulatory surgery for vascular access of hemodialysis patients may help improve the efficiency of vascular access surgery.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Unusual Ultrasound Graft Finding
Christy Gossett, Wisit Cheungpasitporn, Andrea G. Kattah, Fawad Qureshi. Mayo Clinic Minnesota, Rochester, MN.

Introduction: 42-year-old female with ESKD, dialysis dependent for 5 years, presented to ER feeling unwell and hyperkalemic to 6.8 mmol/L. Due for dialysis that morning but no missed dialysis sessions recently. Access is a right brachial artery to brachial vein loop graft created about 4 months ago. Graft had been difficult to cannulate with elevated pressures and pain requiring a decrease in blood flow rate or early treatment termination.

Case Description: Bruit, thrill and subcutaneous edema of the right arm overlying the graft noted. US revealed patent graft but unexpected findings of three adjacent fistulous communications between the distal loop graft and a superficially overlying subcutaneous branch of the right cephalic vein (figure 1). No surgical intervention recommended by Vascular Surgery. Repeat US done to mark patient’s arm with cannulation sites resulted in successful cannulation and patient discharge. 1 month later, patient readmitted with similar presentation as markings not been preserved and cannulation challenges recurred. More extensive markings were created, identifying the overlying vein as well as cannulation sites. Patient refused further use of the graft and required central venous catheter placement.

Discussion: We describe an unusual case of difficult AV graft cannulation due to overlying cephalic vein. Cannulation improved with skin marking to guide cannulation, though due to impermanence of the markings, rehospitalization occurred and central catheter placement was required due to patient refusal to allow further graft cannulation. Early assessment of cannulation challenges with diagnostic US in patent dialysis fistulas or grafts may identify unexpected causes of cannulation. US and skin marking is a potential means of improving cannulation difficulties and avoid central catheter placement in unusual cases, such as described.
Methods: The effect of an online, 30-minute, CME-certified 2-expert discussion was analyzed vs the effectiveness of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar’s test at the question level (5% significance level, P <.05) assessed educational effect. The activity launched January 5, 2021 and data were collected through March 25, 2021. 

Results: In total, 354 nephs and 334 PCPs answered all pre-/post-assessment questions and were included in the study. Overall, 54% of nephs and 38% of PCPs improved their knowledge (P<.01 for both groups) 37% of nephs and 23% of PCPs demonstrated improvements at identifying dose requirement comparisons for inflamed vs noninflammed patients (P<.01 for both groups) 17% of nephs and 15% of PCPs demonstrated improvements at recognizing clinical trial data related to safety for emerging HIF PHIs (P<.05 for both groups) 13% of nephs and 12% of PCPs demonstrated improvements at recognizing clinical trial data related to iron status for emerging HIF PHIs (P<.05 for both groups) 54% of nephs and 46% of PCPs reported increased confidence in knowledge of HIF-PHIs in the treatment of anemia in patients with CKD who are iron replete or nonreplete Continued gaps: 35% of nephs and 54% of PCPs need additional education related to identifying disease management comparisons for inflamed vs noninflammed patients 56% of nephs and 70% of PCPs need additional education related to recognizing clinical trial data for emerging HIF PHIs 23% of nephs and 50% of PCPs need additional education related to recognizing clinical trial data related to iron status for emerging HIF PHIs

Conclusions: This study demonstrates the success of online, video-based 2-expert discussion on improving knowledge of nephs and PCPs related to HIF-PHIs for the treatment of anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca ad Fibrogen

PUBLIC40

Success of Online CME at Improving Nephrologist Understanding of Strategies to Reduce Progression of CKD

Background: Clinicians need good clinical understanding of new strategies for slowing the progression of CKD. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists and primary care physicians (PCPs) related to use of SGLT2 inhibitors to reduce the progression of CKD.

Methods: The effect of an online, 30-minute, CME-certified 3 faculty roundtable discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar’s test was conducted to assess significance at the question level (5% significance level, P <.05) assessed educational effect. The activity launched November 30, 2020 and data were collected through February 22, 2021.

Results: In total, 307 nephrologists and 224 PCPs answered all pre-/post-assessment questions and were included in the study Overall improvements were seen after participation in both CME activities: 16% of nephrologists and 21% of PCPs demonstrated improvements at identifying clinical trial data for SGLT2 inhibitors in the reduction of CKD progression (P<.05 for both groups) 9% of nephrologists and 11% of PCPs demonstrated improvements at adjusting therapy in a patient needing enhanced renal protection (P<.01 for nephrologists, P<.05 for PCPs) 40% of nephrologists and 39% of PCPs had a measurable increase in confidence in knowledge of renal benefits of SGLT2 inhibitors Continued educational gaps: 27% of nephrologists and 41% of PCPs need additional education related to clinical trial data for SGLT2 inhibitors in the reduction of CKD progression

Conclusions: This study demonstrates the success of online, video-based roundtable panel discussion on improving knowledge of nephrologists and PCPs related to use of SGLT2 inhibitors to reduce the progression of CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca

PUBLIC41

Online Video-Based CME Successful at Improving Knowledge of Nephrologists Related to Mineralocorticoid Receptor Antagonists for CKD in Type 2 Diabetes

Background: One goal of continuing medical education (CME) is improving knowledge related to mechanisms of action for new therapeutic options. We sought to determine if a video-based CME activity could improve the knowledge of nephrologists related to the mechanism of action of nonsteroidal mineralocorticoid receptor antagonists (MRAs) in the management of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D).

Methods: The online CME activity consisted of a 30-minute, video-based presentation by 1 expert faculty using green screen technology to enhance the visual presentation related to mechanism of action. To measure outcomes, a repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar’s test at the question level (P<.05 is considered significant) assessed statistical significance. The activity launched in December 2020 and data were collected through March 2021.

Conclusions: This study demonstrates the success of online, video-based presentation using green screen technology on improving knowledge of nephrologists related to mechanism of action of nonsteroidal MRAs in managing CKD in T2D. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Buyer

PUBLIC42

Success of Online CME Improving Nephrologists’ Knowledge Related to Drug Agents for Hepatorenal Syndrome
Amy Larkin, Donald Blatherwick, George Boutsalis. Medscape Education, New York, NY.

Background: Clinicians need to understand clinical profiles of emerging agents in order to use safely and effectively when available to improve their patient management of HRS. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists related to emerging treatments for HRS.

Methods: This study demonstrates the success of online CME in improving nephrologists’ knowledge and self-efficacy confidence in recognizing clinical trial data for emerging treatments for HRS: A total of 324 nephrologists answered all pre-/post-assessment questions and were included in the study. McNemar’s test at the question level (5% significance level, P <.05) assessed educational effect. The activity launched January 5, 2021 and data were collected through April 12, 2021.

Results: In total, 324 nephrologists answered all pre-/post-assessment questions and were included in the study. Overall, 35% of responses improved from pre-to-post (P<.001) On a question level: 12% of nephrologists improved at recognizing clinical trial data for an emerging treatment options for HRS 27% of nephrologists improved at acute kidney injury (AKI) in a patient with cirrhosis 5% of nephrologists improved at selecting the next step in treatment for a patient with HRS Overall, 58% of nephrologists had a measurable improvement in confidence in your knowledge of emerging treatment options for patients diagnosed with HRS-AKI, for an average confidence shift of >70% Continued educational gaps: 35% of nephrologists did not recognize clinical trial data for an emerging treatment option 16% of nephrologists did not recognize AKI in a patient with cirrhosis

Conclusions: This study demonstrates the success of an online summary from a satellite symposium on improving management of HRS by nephrologists. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Mallinckrodt

PUBLIC43

Online CME Is Successful in Prompting Performance Improvements Related to Hyperkalemia Management
Amy Larkin, Donald Blatherwick, George Boutsalis. Medscape Education, New York, NY.

Background: We studied the effect of online education designed to improve the clinical performance of nephrologists, cardiologists, and NPs/PAs related to hyperkalemia management to enable/optimize RAAS inhibitor use.

Methods: The CME activity was a 30-minute online video roundtable panel discussion between 3 experts. Faculty discussion was reinforced with synchronized slides presenting supportive data. The impact of the education on performance outcomes was measured with a survey immediately post-education to assess planned changes in clinician practice as a result of participation in CME activity. Survey participants were contacted 8 weeks later to conduct a self-reported actual change in practice. The activity launched October 6, 2020 and data were collected through April 30, 2021.

Results: A total of 275 clinicians completed the survey immediately post-education (91 nephrologists, 75 cardiologists, 109 NPs/PAs) 19% of nephrologists, 8% of cardiologists, and 4% of NPs/PAs reported actual changes in practice vs noninflammed patients (P<.01 for both groups) 63% of nephrologists, 40% of cardiologists, and 42% of NPs/PAs are in private practice 44% of nephrologists, 64% of cardiologists, and 36% of NPs/PAs reported being in a suburban location 91% of respondents indicated an average of 3.2 planned practice changes Each clinician contacted 28 clinicians who completed the follow-up survey (12 nephrologists, 6 cardiologists, 10 NPs/PAs) Of those, 86% reported making an average of 3.9 changes in practice as a result of this activity. Changes in practice include: Consider a loop diuretic as the initial treatment in hyperkalemia contributing to hyperkalemia (58% nephrologists, 83% cardiologists, 70% NPs/PAs) Reviewing medications and diet to identify factors contributing to hyperkalemia (58% nephrologists, 83% cardiologists, 70% NPs/PAs) Controlling hyperkalemia with a novel potassium binder to optimize dose of RAAS inhibitors (58% nephrologists, 33% cardiologists, 50% NPs/PAs) Using patimotro in patients on spironolactone to maintain normokalemia and allow for spironolactone continuation and dose up titration, per the PEARL-HF Study (58% nephrologists, 33% cardiologists, 40% NPs/PAs)
Success of Virtual Patient Simulation at Improving Diagnosis and Management of Chronic Hyperkalemia

Amy Larkin, Donald Blatherwick. Medscape Education, New York, NY.

Background: We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists (neph) and primary care physicians (PCPs) related to quality of life issues in patients with metabolic acidosis and emerging treatments options.

Methods: The effect of online, 30-minute, CME-certified 2-expert discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design, paired samples t-test for overall and McNemar’s test at the question level (5% significance level, P < 0.05) assessed educational effect. The activity posted November 4, 2020, and data were collected through January 27, 2021.

Results: In total, 416 nephs and 502 PCPs answered all pre-/post-assessment questions. There were included in the study. Overall improvements were seen after participation in both CME activities: Overall, 44% of nephs and 53% of PCPs improved their knowledge (P < 0.01 for both groups) 8% of nephs and 25% of PCPs demonstrated improvements identifying signs of excess acid retention (P = NS for nephs, P < 0.01 for PCPs) 23% of nephs and 19% of PCPs demonstrated improvements identifying effect of increasing sodium bicarb in patients with chronic kidney disease and metabolic acidosis (P = NS for nephs, P < 0.01 for PCPs) 26% of nephs and 30% of PCPs demonstrated improvements recognizing effect of emerging treatment for metabolic acidosis (P = NS for both groups) 36% of nephs and 45% of PCPs had a measurable improvement in confidence discussing QOL concerns with metabolic acidosis (P < 0.01 for both groups) Continued educational gaps: 19% of nephs and 39% of PCPs need additional education related to identifying excess acid retention 42% of nephs and 55% of PCPs need additional education related to effect of increasing sodium bicarb in patients with CKD and metabolic acidosis 38% of nephs and 52% of PCPs need additional education related to data on emerging treatment options for metabolic acidosis.

Conclusions: This study demonstrates the success of online, video-based 2-expert discussion on improving knowledge of nephs and PCPs related to QOL issues with metabolic acidosis and emerging treatment options. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Vifor

Nephrology Best Practice, Integrating Healthcare Education, and CKD: A Qualitative Perspective

Shahid N. Muhammad, 1,2 The University of the West of England (UWE), England UK, Bristol, United Kingdom; The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.

Background: Education and information seeking is pinnacle for patients with Long-Term Conditions (LTCs) like Chronic Kidney Disease (CKD) to take ownership of health and disease and navigate healthcare between health sectors. Patient and Public Involvement (PPI) is key to help understand gaps in health education. 1) Involving patients between two support groups to help understand which topics and subjects are pertinent to CKD patients; 2) Involving patients to understand whether, retrospectively there has been an educational neglect in healthcare; and 3) To understand how healthcare and education for CKD patients could be more integrated.

Methods: Two PPI workshops were implemented (May and June 2019) after reviewing NIHR INVOLVE best practice guidelines. Fourteen (14) topic tags were applied over 1-month (March and April 2020) between the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDARs) (est.2014) for Kids platforms. Group dismantlers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection.

Results: Thematic Analysis was used to highlight findings, according to over-arching themes having used Nvivo-12 software to code and help understand where there are healthcare educational inefficiencies. Five themes were identified through this study including: 1) Bridging Educational Gaps through Different Mediums - 'Relaying Knowledge through Healthcare'; 2) Reliability and Validity of using the Internet to Collect Data; 3) Healthcare, Patient and Public Involvement and Maintaining Confidentiality through Online Methods to collect Qualitative Data; 4) Advantages, Disadvantages and Limitations to Online Data Collection and Peer Support Groups; 5) Using Qualitative Methodology to Understand Educational Needs for CKD Patients.

Conclusions: Wider Allied Health Professionals (AHPs) could increasingly find themselves taking on roles, particularly where involvement is increasingly dependent bridging educational gaps and ‘alleviating misinformation’ through technology and ‘online spaces’.

What, If Any, Are the Nephrology Health Educational Needs of CKD Patients: A Qualitative Inquiry

Shahid N. Muhammad. 1The University of the West of England (UWE), England UK, Bristol, United Kingdom; The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.

Background: An estimated 15 million patients in England have at least one Long-Term Conditions with the prevalence of CKD rising. The characterization of CKD at all stages is an important part of its management and allows the initiation of appropriate treatments with the aim of slow progression of kidney disease. Providing up-to-date, accurate health education is pinnacle for patients to take ownership of healthcare. Patients require educational support as part of healthcare and help navigate understanding with different healthcare professionals. The aims and objectives of this research was to understand how CKD patients should be encouraged to take ownership of healthcare through education.

Methods: The theoretical framework for this research involved an Inductive Content Analysis (ICA) approach where essentially qualitative data collection and analyses will help understand what if any, are the health educational needs getting perspectives from CKD patients and Health Professionals (HPs). ICA is particularly effective to help understand analysis in linking theory, or framework,19 participants between 4 cohorts, that included 6 General Practitioner (GPs), 4 Healthcare Scientists (HS), and 6 CKD Patients (CKDPs) were recruited and participated in telephone interviews.

Results: Majority of CKDPs were in between CKD4 and CKD5. Interviews allowed participants to put forward views and understanding, relating to healthcare education. Topic guides were developed for participant cohorts with several themes to collect data through one-to-one telephone interviews. NViVo-12 software provided opportunity to classify and arrange transcript context and glean insight to develop overall conclusions. Nine (9) main themes and several sub-themes were identified when coding for healthcare professionals (HPs), and Nine (9) main themes and several sub-themes identified when coding qualitative data for patients (CKDPs).

Conclusions: There needs to be a coordinated effort between patients and professionals, to understand how CKD education is more integrated with healthcare, and especially wherein involvement is end-to-end. This exploratory study provides evidence applying research to public health. Every effort has been made to reduce biases and diminish disparities. Point of Care Education (POCE) could be an integrated through online spaces and linked to Electronic Patient Records (EPRs).
Chronic Hyponatremia: Challenges in Diagnosis and Management
Shivangi Patel, Atlantic Health System Inc, Florham Park, NJ.

Introduction: Hyponatremia is manifestation of variety of disorders. Hyponatremia occurs as result of water intake exceeds greater than water excretion. Management becomes a challenge due to etiology and costly drugs.

Case Description: 46-year-old male computer engineer who exercises 3 times a week, takes 25 grams of protein shake daily with no past medical history, not on meds, noted to have chronic sodium of ~126 mEq/L with stable BMI 26. His only complaint was mild fatigue. His exam was normal with a negative orthostatic. Labs: Sodium 126 mEq/L, Potassium 3.6 mEq/L, uric acid 2.8 mEq/L, Creatinine 0.65 mg/dL, Serum Osmolality 266 mOsm/kg, Urine sodium 72 mEq/L, Urine potassium 60.1 mEq/L specific gravity 1.018, Urine Osmolality, 626 mOsm/kg H2O and 200 mOsm/L Renal, adrenal, and thyroid function are normal. Imaging of brain, chest and abdomen is negative for pathology. He underwent colonooscopy with surup which provided the least amount of volume load and ure-Na prescribed to keep his serum sodium stable during the bowel prep. Max sodium achieved was 130 mEq/L after 3 g of Ure-Na. It was discovered later, his brother was noted to have sodium of 115 diagnosed at age 20 and maintained on sodium bicarb but was never tested genetically, nor achieved normal sodium levels.

Discussion: Labs were consistent with SIADH however he had undetectable copeptin level and negative workup for malignancy. Due to family history with negative workup for any other etiology, he likely has Nephrogenic Syndrome of Inappropriate Diuresis (NSIAD). NSIAD is caused by gain-of-function mutation in AVP receptor type 2 located on long arm of X chromosome (Xq28). Genetic confirmation for NSIAD is pending and if positive will need to test other family members. Management for chronic hyponatremia was challenging as fluid restriction was not feasible to adhere to as suggested by his high urine (Na,K) and high urine osmolality ~ 500mOsm/kg. Ure-Na was useful at time of bowel prep to avoid worsening of hyponatremia, however never achieved normal sodium even after 30 g of Ure-Na. Vaptans were not tried as are more costly than Ure-Na and unclear efficacy in NSAID. Patient did not want to pay $80 of Urena, and he increased his protein intake to 75 g daily with fluid restriction 1.5 L/day, which maintained his sodium level at 130.

Spontaneous Regression of Hyperammonemic Encephalopathy, Lactic Acidosis, Gastric Mucosa Injury, and Hepatic Portal Venous Gas After Infusion of 5-Fluorouracil
Yoshihiro Nakamura,1 Yotohashi-shi, Yotohashi, Japan; Chubu Rosai Byoin, Nagoya, Japan.

Introduction: 5-fluorouracil (5-FU) therapy is associated with hyperammonemic encephalopathy and lactic acidosis. 5-FU has a direct toxic effect on the gastric mucosa. Hepatic portal venous gas (HPVG) is caused by various factors including bowel necrosis and gastrointestinal ulcers.

Case Description: A 79-year-old man was referred to the nephrology department owing to lactic acidosis. He had a history of hypopharyngeal carcinoma. Two days prior to the consultation, he was started on 300 mg of carboplatin and 4000 mg/m² of 5-FU as a continuous intravenous infusion. On the consultation day (day 1), he was experiencing confusion and had a GCS score of 11/15. There was a significant increase in NH₃ (>500 µg/dL) and lactate levels (19 mmol/L). Urine sodium was 72 mEq/L, Urine potassium 60.1 mEq/L specific gravity 1.018, Urine Osmolality, 626 mOsm/kg H₂O and 200 mOsm/L Renal, adrenal, and thyroid function are normal. Imaging of brain, chest and abdomen is negative for pathology. He underwent colonoscopy with suprap which provided the least amount of volume load and Ure-Na prescribed to keep his serum sodium stable during the bowel prep. Max sodium achieved was 130 mEq/L after 3 g of Ure-Na. It was discovered later, his brother was noted to have sodium of 115 diagnosed at age 20 and maintained on sodium bicarb but was never tested genetically, nor achieved normal sodium levels.

Discussion: Labs were consistent with SIADH however he had undetectable copeptin level and negative workup for malignancy. Due to family history with negative workup for any other etiology, he likely has Nephrogenic Syndrome of Inappropriate Diuresis (NSIAD). NSIAD is caused by gain-of-function mutation in AVP receptor type 2 located on long arm of X chromosome (Xq28). Genetic confirmation for NSIAD is pending and if positive will need to test other family members. Management for chronic hyponatremia was challenging as fluid restriction was not feasible to adhere to as suggested by his high urine (Na,K) and high urine osmolality ~ 500mOsm/kg. Ure-Na was useful at time of bowel prep to avoid worsening of hyponatremia, however never achieved normal sodium even after 30 g of Ure-Na. Vaptans were not tried as are more costly than Ure-Na and unclear efficacy in NSAID. Patient did not want to pay $80 of Urena, and he increased his protein intake to 75 g daily with fluid restriction 1.5 L/day, which maintained his sodium level at 130.

Methanol Poisoning Diagnosed by Brain MRI
Abhinaya Sridhar,1 Viviam I. Becerra Rivera,2,3 Savneek S. Chugh.1
1Westchester Medical Center, Valhalla, NY; 2New York Medical College, Valhalla, NY.

Introduction: Methanol poisoning is deadly yet remains relatively common. Delays in diagnosis increases the risk of irreversible organ damage and death. In the absence of serum or urine levels, radiological findings may be useful in diagnosis. We report a unique case of methanol toxicity where we made the diagnosis based on characteristic brain MRI findings as timely serum or urine levels were unavailable.

Case Description: 81-year-old woman presented with altered mental status, poor appetite, lethargy and two episodes of vomiting en-route to the emergency room. On examination, her vital signs were normal but she was mildly agitated, oriented to person only. Initial blood work was significant for a low Bicarbonate level of 10mEq/L, Anion Gap 22, creatinine 0.81 mg/dL, serum Osmolality 403 mOsm/kg with calculated osmolality 290 mOsm/kg and Arterial Blood Gas (ABG) showing pH 7.29 and pCO₂ 24. Her CT head showed no acute changes with white matter microvascular ischemic disease. Because of high osmolar gap anion gap metabolic acidosis, patient was given intravenous Fomepizole. Overnight, her condition deteriorated requiring intubation and mechanical ventilation. Her repeat ABG showed worsening acidosis with pH 6.9 and pCO₂ 19. She was subsequently started on sodium bicarbonate drip. Further work up was negative for serum methanol, ethanol, salicylate, blood alcohol and 5-oxo-proline levels. Her acidosis gradually improved but her mental status continued to remain poor for which she had a brain MRI which showed extensive parenchymal brain abnormality, leukoencephalopathy and basal ganglia involvement reminiscent of acute methanol toxicity and thus a diagnosis was made. Unfortunately, her mental status remained poor and after consulting with palliative care, decision was made to prioritize patient comfort and terminal extubation.

Discussion: Characteristic MRI findings in methanol toxicity are high T2 signal suggest the presence of narcotics of lentiform nucleus with predilection for the putamen. There may be necrosis of lobar white matter with sparing of subcortical fibers and hemorrhagic transformation. Our patient had similar findings as well. An extensive ingestion history is crucial when evaluating high osmolar gap. However, in the absence of timely blood work and ingestion history, like in our patient, brain imaging with MRI may be integral to diagnosing methanol poisoning.
Online Dysnatremia Correction Calculators: Consistency and Practice Guideline Adherence
Christina M. Yuan,1 Maura A. Watson,1 Benjamin M. Forster,2 James D. Oliver,1
1Walter Reed National Military Medical Center, Bethesda, MD; 2William Beaumont Army Medical Center, El Paso, TX.

Background: Online calculators for sodium correction in dysnatremia are frequently used by non-nephrologists. We assessed 5 popular calculators which use the Androgue-Madigs equation for practice guideline adherence and reproducibility in a theoretical 80 year old, 100 kg (72 inch) male.

Methods: Hyponatremia case: Na+ 150 mEq/L. Guideline-based Rx: Estimated water deficit 4.2 L. Replacement target 2.1 L. In the first 24 hours, plus 1.5 L insensible losses. Infusate: 150 ml/hr D5W. Hyponatremia case: Na+ 115 mEq/L, euclidean with acute/severe symptoms, normal serum K+. Guideline-based Rx: Immediate treatment: 3% NaCl, 100 ml over 10 minutes up to 3 times; Na+ and infusate rate redetermination.

Calculated rate of 3% NaCl: range 32-64 mL/hr. Only 1 calculator incorporated infusate adjustments. Calculated rate that exceed safe correction rate; 4/5 had no discussion of chronicity, symptom severity, or need for frequent Na+ determination/infusate rate recalculations. These may contribute to unexpected adverse outcomes. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Results: See Table. On-line Calculators for Hyponatremia: Water deficit calculated in 3 (range 3.6-4.3L). Insensible loss calculated in 1. Replacement target defaults: 140-145 mEq/L Na+ at 10-24 hours. On-line Calculators for Hyponatremia: One discusses volume status, acuity, and symptoms. Only 2 indicate rapid correction should be used for severe symptoms. Default correction rate range: 6-12 mEq/L/day. These may yield rates that exceed safe correction rate; 4/5 had no discussion of chronicity, symptom severity, or need for frequent Na+ determination/infusate rate recalculations. These may contribute to unexpected adverse outcomes.

Conclusions: The 5 calculators correctly use the Androgue-Madigs equation to determine infusate rate of hypertonic or hypotonic fluids in dysnatremia. However, defaults in treatment may yield rates that exceed safe correction rate; 4/5 had no discussion of chronicity, symptom severity, or need for frequent Na+ determination/infusate rate recalculations. These may contribute to unexpected adverse outcomes. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Comparison of Online Calculator Results with Guidelines

PUB153
Mass Poisoning from Ethylene Glycol at a US Military Base
Nina Shah, Benjamin M. Forster, Sarah Petteys, Scott B. Sullivan. William Beaumont Army Medical Center, El Paso, TX.

Introduction: Ethylene glycol (EG) poisoning occurs over 5000 times annually in the US, but a poisoning outbreak (3 cases within 72 hours) has not previously been reported. We describe on an EG poisoning outbreak in January 2021, presenting at William Beaumont Army Medical Center.

Case Description: Eleven soldiers presented to the emergency room over a twelve hour period after ingestion of an unknown alcoholic beverage. All were 18 years old, except one 17 year old, 100 kg (72 inch) male. Two patients with elevated Lac received bicarbonate-based intravenous fluids (IVF) and FOM. Two patients received IVF only and required prolonged observation for worsening acidosis and/or AKI. Five patients with normal lab values were treated with IVF and observation. All patients received cofactors including thiamine and pyridoxine. All patients survived. The outbreak occurred in the setting of limited dialysis resources and FOM availability and in a community with widespread COVID-19 activity. Additional guidelines are needed to determine allocation of limited resources and optimal dialysis and FOM treatment course, and identify comorbid conditions which may prolong recovery.

Discussion: Two patients received immediate hemodialysis (HD) in combination with fomepizole (FOM) due to severe acidosis plus elevated OG and AG (Table). These patients developed acute kidney injury (AKI) with renal recovery occurring within a 3-week period. Two patients with elevated Lac received bicarbonate-based intravenous fluids (IVF) and FOM. Two patients received IVF only and required prolonged observation for worsening acidosis and/or AKI. Five patients with normal lab values were treated with IVF and observation. All patients received cofactors including thiamine and pyridoxine. All patients survived. The outbreak occurred in the setting of limited dialysis resources and FOM availability and in a community with widespread COVID-19 activity. Additional guidelines are needed to determine allocation of limited resources and optimal dialysis and FOM treatment course, and identify comorbid conditions which may prolong recovery. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

809
Case Description: Our patient presented with abnormal labs (Table 1). She had no urinary frequency, abdominal pain, nausea, vomiting, constipation, or confusion on admission. She had mild pruritus and bilateral plantar foot pain and elbow pain. Her EKG was unremarkable. She received 2 liters of 0.9% saline and was started on continuous 0.9% saline intravenous fluids at 150 mL/hour upon admission. She drank a half-gallon of milk per day for the last two years. She consumed a Premier protein shake each morning with breakfast, which contains 50% of the daily value (DV) of calcium and 25% of the DV of Vitamin D. She rarely took antacids. She had a multivitamin containing 100% of the DV of Vitamin D and an additional Vitamin D supplement. Review of systems was positive for episodes of polyuria, urinary frequency, and dry mouth, for which she compensated with large volume fluid intake.

Discussion: Our patient was diagnosed with chronic milk-alkali syndrome. This syndrome is characterized by hypercalcemia, hyperphosphatemia, metabolic alkalosis, AKI and metastatic calcification. Hypercalcemia causes vasocostriction, which decreases the glomerular filtration rate (GFR). It suppresses PTH secretion and leads to renal retention of phosphate. It activates the calcium-sensing receptor (CaSR) at the basolateral surface of Loop of Henle cells, inhibiting Na-K-2Cl co-transporter, enhancing natriuresis and inducing volume depletion, which augments proximal reabsorption of calcium and bicarbonate. Alkalosis activates the pH-sensitive calcium channel, TRPV5, in the distal nephron, thereby contributing to calcium retention and hypercalcemia. Standard treatment is withdrawal of exogenous calcium and administration of intravenous normal saline. Furosemide is sometimes used in severe cases.

Lab Results

<table>
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Our patient was diagnosed with chronic milk-alkali syndrome. This syndrome is characterized by hypercalcemia, hyperphosphatemia, metabolic alkalosis, AKI and metastatic calcification. Hypercalcemia causes vasocostriction, which decreases the glomerular filtration rate (GFR). It suppresses PTH secretion and leads to renal retention of phosphate. It activates the calcium-sensing receptor (CaSR) at the basolateral surface of Loop of Henle cells, inhibiting Na-K-2Cl co-transporter, enhancing natriuresis and inducing volume depletion, which augments proximal reabsorption of calcium and bicarbonate. Alkalosis activates the pH-sensitive calcium channel, TRPV5, in the distal nephron, thereby contributing to calcium retention and hypercalcemia. Standard treatment is withdrawal of exogenous calcium and administration of intravenous normal saline. Furosemide is sometimes used in severe cases.

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PUB159

Successful Therapy for Life-Threatening Hyperkalemia with Isotonic Sodium Bicarbonate and No Dialysis

Vijayakumar Paramasivam, Daniel G. Gomez, Spencer Hodgins, Daniel L. Landry, Gregory L. Braden. UMass/Baystate, Springfield, MA.

Introduction: Isotonic sodium bicarbonate (ISB) intravenously (iv) alone in acidicotic pts was shown by K Schwarz, Circulation, 19:215, 1959 & Adler and Fraley in Kid Int, 12: 354, 1977 to cause up to a 3 mEq/L decrease in serum potassium (K) within 4 hours when K>5.0 and iv ISB was given. We treated a pt with a serum of K 9.8 mEq/L in near in 14 hrs.

Case Description: A 90 yr old woman with Type 2 diabetes presented in sine wave, HR 100/min & systolic BP 80 mmHg with a K of 9.8 mEq/L. She ha3 mEq/La baseline serum creatinine of 1.6 mg/dl with a K of 6.2 mEq/L & serum bicarbonate of 19 mEq/L. She was started on trimethoprim/sulfa 1 week earlier. Admission labs showed (mEq/L): Na: 141, K 9.8, Cl 108, HCO3-13, serum creatinine 3.6 mg/dl, pt 7.2, UNA 43 mEq/L, UK 31 mEq/L, FE NA 1.8% & TTKG 0.5. The family & pt refused dialysis. She was given 3 amps of iv 10% calcium gluconate & her EKG converted to sinus rhythm. ISB (150 mEq of Na & bicarbonate/L) was started at 150 ml/hr along with sodium polystyrene resin 60 gm every 6 hours & 1 amp of Dextrose 50% (25 gm) followed by 10 U of regular insulin every 4 hrs. Labs in mEq/L showed: After 5 hrs: Na, 145 K 7.8, Bicarb 16, glucose 156 mg/dl. After 10 hrs: Na135, K 6.8, Bicarb 20 glucose 185 gm/dl. After 14 hrs: Na 135, K 5.5, Bicarb 21 glucose 248 mg/dl. After 24 hrs: Na 142, K 3.3, Bicarb 28 glucose 157mg/dl, & TTKG 44.

Discussion: Our pt showed a 2 mEq/L decrease in serum K 5 h after a fast drip infusion rate of ISB giving 112 m of ISB, a 3 mEq/L decrease after 225 m of ISB & 4.3 mEq/L after 315 m of ISB plus iv dextrose and regular insulin every 4 h. Sodium polystyrene resin works after 6 h and helped lower the serum K. The low TTKG at the different times shows that increased renal excretion did not account for the dramatic decrease in serum K. We Conclude: In acidotic pts ISB by continuous iv infusion along with q 4h iv dextrose and insulin can successfully reverse life threatening hyperkalemia without dialysis.

PUB160

An Interesting Case of Non-Anion Gap Metabolic Acidosis Secondary to Arginine Hydrochloride Infusion Therapy

Jwanjot K. Narula, Kiran Shivraj, Angela Y. Kim, Nadera Rahman, Amol Mittal. Westchester Medical Center, Valhalla, NY.

Introduction: Mitochondrial disorders are relatively common inherited disorders, the syndrome of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a disorder characterized by hemiparesis, cortical blindness, or hemianopia, muscle weakness, seizures. Treatment of MELAS is critical, delay may result in cortical injuries, neurologic dysfunction and ultimately dementia. The pathophysiology involves reduced vasodilation. L-Arginine is a precursors to nitric oxide, which mediates vasodilation. Despite widespread use of arginine hydrochloride, there is limited understanding of its adverse effects, particularly metabolic acidosis.

Case Description: In our case report, we present a 60 year old male with MELAS who was brought in due to a 3 week progressive weakness, falls associated with poor appetite and failure to thrive. In the hospital, he became encephalopathic with RLL Aspiration pneumonia. Head CT showed ischemic changes. He was started on 30mg IV arginine HCl in 300ml of NS over 90 minutes. Day 1 of infusion, he developed hyperchloremic non anion gap metabolic acidosis with hyperkalemia. Due to hyperkalemia refractory to medical management and development of nonoliguric AKI due to ischemic ATN, the patient was started on CVVHD. His renal function recovered after two days with no further indications to continue dialysis, hypotension had also resolved with removal of vasopressor support.

Discussion: The pathogenesis of clinical features in MELAS has been attributed to the energy defect, causing dysfunction of the microcirculation thus poor perfusion. In our patient, who had hyperperfusion and encephalopathy, L-Arginine was the ideal treatment. The recommended infusion is standardized in adults. We suspect in our patient, the renal impairment resulted in the loss of renal excretion of bicarbonate combined with the relatively high arginine dose due to low body surface area resulted in severe acidosis. To prevent metabolic acidosis with the infusion of Arginine HCl, it should be dosed as per the BSA with close monitoring of the pH. The ability of the kidney to acidify the urine should be monitored by directly measuring the urine ammonia or the surrogate method like Urine anion gap or urine pH.

PUB161

Adrenal Tumor Causing Hyperaldosteronism Leading to Kaliopenic Amol

Jiwanjot K. Narula, Kiran Shivraj, Angela Y. Kim, Nadera Rahman, Amol Mittal. Westchester Medical Center, Valhalla, NY.

Introduction: Nephrocalcinosis is of rare occurrence in a patient with cystic renal disease, nephrocalcinosis and nephrolithiasis. Blessey S. Bhalia, Rajesh K. Aggarwal, Tribhalaji Action Medical Institute, Pashim Vihar, New Delhi, India.

Case Description: 50 years old female presented with history of weight loss and hypokalemia. She had nocturia, polyuria without the counter, herbal medicine use. She was on antihypertensive drugs including temelisartan. Recent records showed persistent hyperkalemia in the range of 0.7 0.3 mEq/L. BP160/100 mm of hg without any postural drop. Abg showed metabolic alkalosis. Her urinary osmolality was 184mosm/kg with urinary ph 5.5. 24 hour urine uric acid 3.5 L. Urinary sodium 200 mg, potassium160 mg, chloride250 mg, creatinine 30 mg/day (>40 mg/d) creatinine 800 mg/dl 20 mg/dl). Calcium260 mg/dl 4 mg/kg/d, uric acid 300 mg/dl 170-300 mg/dl, phosphate 20 mmol/d (13-40 mmol/d) TTKG was 9.5. Her aldosterone to renin ratio 36.8 90.1 (<15).

Discussion: An MRI abdomen showed bilateral normal sized cystic kidneys with wall calcification and nephrocalcinosis bilateral renal stones and left adrenal mass lesion of the size of 4.1x3.5 cm which was heterogeneously hypointense on out of phase imaging suggestive of malignant etiologya and a lytic lesion in L3 vertebrae. The patient had been advised adrenolecctomy and has been started on tab spironolactone and potassium citrate.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

811
potential subjects and establish rapport. Native-language welcome packets that included information on the dedicated services and mapped out home care visit requests/expectations were created. Diverse and inclusive enrollment and retention rates will be compared to prior rare disease trials upon completion of the 12-week ARENA2 study.

Conclusions: Industry-sponsored, culturally sensitive, bilingual patient navigators are key stakeholders in clinical trials for rare disorders, especially DCs, and can help reduce ethnic and racial disparities. The ARENA2 trial, will analyze and report on the presenting author’s role impacting trial enrollment and retention of Spanish and French speaking populations by addressing complex problems in underrepresented populations.

Funding: Commercial Support- Advicene

PUB163
The Prevalence of Hyperkalemia and Associated Risk Factors in a General Population
Xiaohong Fan, Wenling Ye, Jie Ma, Xuemei Li. Peking Union Medical College Hospital, Beijing, China.

Background: Hyperkalemia has been related to the risk of cardiovascular events associated mortality. The object was to determine the epidemiology of hyperkalemia and associated risk factors in a rural Chinese population.

Methods: We performed a cross-sectional study of 10,281 participants in China in 2014. All participants completed a questionnaire, physical examination, and collected venous blood to detect serum creatinine, and inorganic ions (potassium, etc.). First void morning urine was collected to detect the albumin-creatinine ratio (ACR) and urine potassium. Hyper- and hypokalemia were defined as serum potassium levels >5.0 mEq/L and <3.5 mEq/L, respectively.

Results: The mean age of the study population was 55.4±10.0 years; 47.1% were males. The crude prevalence of hyper- and hypokalemia was 9.3% and 3.0%, respectively. The subjects with hyperkalemia had higher urine potassium-creatinine ratio (4.4±2.6 vs. 3.7±2.5, P<0.001) and potassium excretion fraction (60.1±48.9 vs. 54.1±46.6, P<0.001). In multivariate analyses, the individuals with decreased eGFR<60ml/min/1.73m² had a 3.17-fold increase in the odds of having hyperkalemia. Hypertension, diabetes, and high low-density lipoproteinemia (LDL) were significantly associated with the increased risk of hyperkalemia. However, the female was negatively associated with hyperkalemia even after excluding those with decreased eGFR. The ACEI use was not found to be independently related to hyperkalemia.

Conclusions: The male and participants with hypertension, diabetes and high LDL had an increased risk of having hyperkalemia. Physicians should raise awareness of high-risk groups.

Factors associated with hyperkalemia in the general population

PUB164
A Suspected Case of Cerebral Salt Wasting (CSW) Syndrome in a Patient with Traumatic Subdural Hematoma: Revisiting a Long Debated Topic
Karim T. Attia, Jessica M. Grecco. The Ohio State University Wexner Medical Center, Columbus, OH.

Introduction: It has long been debated whether CSW is a true entity causing hyponatremia in patients with central nervous system (CNS) pathology or whether the hyponatremia is actually secondary to SIADH while apparent salt wasting is due to underappreciated volume expansion. Literature agrees, for the most part, that CSW is a separate disease process and it has been mostly described in patients with aneurysmal subarachnoid hemorrhage. It has also been described in other forms of CNS pathology underappreciated volume expansion. However, it has long been debated whether CSW is a true entity causing hyponatremia.

Conclusions: In this longitudinal analysis of patients with CKD, serum bicarbonate was not associated with the development of gout.

Funding: Commercial Support - Tricida, Inc.

PUB166
Hyponatremia in a Patient with Chyle Leak
Harish C. Nuthakkhi, UT, Houston, TX.

Introduction: Chylous ascites can cause a multitude of electrolyte abnormalities. Hyponatremia is not a very common presentation unlike hyponatremia in pts with chylous ascites. Here we present a case of hyponatremia in a patient with chylous ascites and the various management challenges we face while managing the hyponatremia.

Case Description: We present a case of a 75y old female with a history of papillary cancer of the thyroid status post thyroidectomy and left neck dissection, with worsening chyle leak from the surgical site with evidence of local recurrence of cancer with worsening left cervical lymphadenopathy. She presented with hypotension, which was treated by infusing 4L of normal saline over a period of 36 hours. She was also receiving 1.5L of free water daily with her tube feeds, which were 85% free water. On hospital day 3, she developed hypo-osmolar hyponatremia which reached the nadir over the next 48 hours, and nephrology was consulted. Patient’s urine and serum studies showed a high ADH state due to relapsing papillary thyroid cancer. Patient’s chyle leak responded to IV octreotide and a low-fat diet with medium-chain triglyceride supplementation. The hyponatremia resolved with administration of oral sodium chloride tablets once the chyle leak was controlled.

Discussion: Patients with chylous ascites suffer volume depletion who can be a challenge to quantitatively separate the location of the leak. Excessive fluid administration, either isotonic or hypotonic can lead to severe life-threatening hyponatremia in these patients. Physicians should pay attention to the amount free water being administered through tube feeds in these pts with active malignancies as they are prone to high ADH states.
SIADH-Related Hyponatremia due to a Non-Functioning Hemorrhagic Pituitary Adenoma
Saira Sajid, Katerina Hysi, Minesh Khatri, James Drakakis. NYU Winthrop Hospital, Mineola, NY.

Introduction: Determining the etiology of hyponatremia can be challenging. When euvelonic, one needs to consider a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH). This can be classified into two groups: ectopic production of ADH or release from the posterior pituitary gland related to disorders of the central nervous system, pulmonary disorders or drug administration. Mechanisms of posterior pituitary related hyponatremia are usually due to hypopituitarism or dysfunction of the pituitary adrenal axis. More rare, are reports of SIADH in patients with pituitary tumors and normal associated function. This case report aimed to be related to these mechanisms of stress.

Case Description: 39 year old female with no past medical history presented to the emergency department complaining of numbness and tingling of the bilateral upper and lower extremities. Serum sodium was found to be 122 mEq/L. Urine osmolality 971 mOsm/kg and urine sodium 179 mmol/L. An initial CT scan showed fullness of the sella, possibly representing an underlying lesion. Subsequent MRI of the brain revealed a sellar/suprasellar lesion most consistent with a hemorrhagic pituitary adenoma. Neurohormonal axis proved to be intact and the tumor deemed non secreting. As such, the working diagnosis was SIADH caused by mechanical stress and inappropriate ADH release from the posterior pituitary. She was given a low dose (7.5 mg) of Tolvaptan with ensuing rapid correction of sodium, which required administration of DDAVP and D5W to slow down. Ultimately, salt tablets were started to help maintain an acceptable sodium range. Plan is for endoscopic transspenoidal resection of the pituitary mass.

Discussion: The clinical and laboratory features of this case were consistent with SIADH. There was hyponatremia, in the setting of euvelonic and high urine osmolality and urine sodium. Furthermore, the function of the pituitary gland remained normal on biochemical assessment. In such a scenario of increased ADH secretion, it is important to evaluate the anatomical interaction between the pituitary tumor and the hypothalamo-neurohypophyseal system. The tumor may push the pituitary stalk upward leading to mechanical stress and the isolated gland causing inappropriate ADH release. Such a description is a very rare occurrence, but nevertheless need be considered as a cause of SIADH related hyponatremia.

Pub168
Hyponatremia and Hypothyroidism: Association or Causality?
Gouthami Kondapu, Eric Krutel, Joel M. Topf. Ascension St John Hospital, Detroit, MI.

Introduction: Among the various etiologies of hyponatremia, one that is frequently called into question is hypothyroidism. Literature review repeatedly indicates that only the severe state of myxedema coma has a causality with hyponatremia. Data concerning the incidence of hyponatremia in less severe hypothyroidism is conflicting; there is question as to whether there is any causality at all. Here we present a case of hyponatremia that is attributable to severe hypothyroidism without myxedema coma.

Case Description: 71-year-old female with a past medical history of hypothyroidism presented to the hospital following a fall and complaint of generalized weakness. Patient had a serum sodium of 111, initially thought to be SIADH given a low serum uric acid, urine uric acid less than 20, and serum osmolality of 242. However, the patient had TSH of 65.70 munits/mL with T4 less than 0.1 ng/dL. Patient was given normal saline with minimal sodium correction, and subsequently started on 2% NS with a DDAVP clamp. Patient was started on IV levotrioxine for treatment of her severe hyponatremia. After 4 days of IV levotrioxine and hypertonic saline, her serum sodium reached 130, and she was discharged home on maintenance levotrioxine.

Discussion: The mechanism behind hypothyroid-induced hyponatremia is not well understood. Studies have suggested a hypothryoid state causes a decrease in cardiac output and peripheral vascular resistance, leading to decreased renal perfusion and decreased GFR. One study found that in patients with primary hypothyroidism before and after thyroid replacement, all had decreased GFR, with hyponatremia observed in greater than half the subjects. However, another study found hyponatremia to be uncommon in more short term hypothyroidism. Literature review has largely identified hypothyroidism-induced hyponatremia in myxedema coma. However, this patient presented not with symptoms suggestive of myxedema coma, but with an elevated TSH and no other attributable cause of her hyponatremia. Additionally, the low uric acid and urine sodium argue against a decrease in renal perfusion as the cause of ADH release. In summary, though some recent literature calls into question hyponatremia causing hypothyroidism, we present a case of profound hyponatremia in a patient with severe hypothyroidism without myxedema coma, which responded to treatment of her hypothyroidism as well as hypertonic saline.

Pub169
A Rare Case of Low-Dose Cyclophosphamide-Induced Symptomatic Hyponatremia
Sajied Karandish,1 Tsering Dolkar,2 Dawn Maldonado,1 Ishita Bansal,3 Maritza Brown,4 Ayesha Mallick Imam.1 (Mount Sinai Health System, New York, NY; 2Brookdale University Hospital and Medical Center, New York, New York, NY; 3Mount Sinai Hospital, New York, NY; 4Brooklyn Hospital Center, Mineola, NY).

Introduction: We report a case of severe acute symptomatic hyponatremia with generalized tonic clonic seizures after the first cycle of adjuvant chemotherapy with cyclophosphamide.

Case Description: We present a case of 62-year-old woman who was diagnosed with breast cancer and underwent lumpectomy followed by first cycle of chemotherapy with cyclophosphamide, dexamethasone, and doxorubicin. She received low dose, 15 mg/kg or 1,030 mg IV Cyclophosphamide. On the day of chemotherapy her sodium was 144 mEq/L. The next day the patient had a seizure at home. While in the Emergency Department she had another that only high doses of cyclophosphamide (>40 mg/kg) could induce hyponatremia. However, cases of low-dose cyclophosphamide (<20 mg/kg), have been reported, though uncommon. We report a rare case of low dose cyclophosphamide-induced symptomatic hyponatremia. Our patient’s rapid decline of sodium could have precipitated the seizure. Using hypertonic saline, hyponatremia resolved, and symptoms of hyponatremia resolved without neurological deficits. Cyclophosphamide-induced hyponatremia was first reported by Moses et al demonstrating antidiuretic hormone-like effect of Cyclophosphamide to retain water. More recent studies suggest a direct toxic effect of cyclophosphamide on the kidneys causing renal tubular wasting and an antidiuretic hormone-like activity of cyclophosphamide metabolites. Thus, development of SIADH has been accepted as one of the mechanisms for cyclophosphamide-induced hyponatremia. Thus, physicians should have a low threshold to suspect cyclophosphamide-induced hyponatremia which can be life threatening.

Pub170
Von Hippel-Lindau Syndrome (VHL) Associated with a Breast Tumor

Introduction: We present a case of a woman who was incidentally found to have a breast tumor at the same time that she was found to have several other cysts and tumors, and was ultimately found to have Von Hippel Lindau syndrome (VHL). The breast tumor association has not yet been described in VHL.

Case Description: A 21-year-old female presented to another facility with dysphagia and bilateral upper extremity weakness. CT and MRI of the brain demonstrated multiple cysts in the spinal cord extending to the brainstem. Her renal ultrasound findings were read as polycystic kidney disease. The patient underwent C5-C7 laminectomy and resection of the largest intramedullary tumor. Pathology review revealed grade 1 hemangioblastoma. She presented to our hospital 3 months later for dyspnea and tachycardia, so CT angiogram of the chest was performed to rule out pulmonary embolism. It incidentally revealed a right breast mass measuring 3.5x2.7 cm, a 1.9 cm liver lesion, and innumerable sub-centimeter hypodense masses in both kidneys. The dyspnea was attributed to pneumonia and atelectasis from her post-operative recovery. A repeat renal sonogram at our facility demonstrated small kidney cysts, so the diagnosis of PKD was questioned and re-evaluated. Genetic testing ultimately returned positive for VHL-1. Her breast mass was found to be a BIRADS-4A lesion on ultrasound, and core biopsy demonstrated a fibroadenoma.

Discussion: VHL is a rare autosomal dominant disorder characterized by the presence of multiple benign and malignant tumors and a pathogenic variant of the VHL gene. VHL is a tumor suppressor gene that inhibits hypoxia-inducible transcription factor, thereby inhibiting hypoxia-induced vascular growth. Loss-of-function mutations hence lead to tumor growth in multiple organs. Tumors associated with VHL include infrarenalier hemangioblastomas, renal cysts and angiomylipomas, and thyroid cysts. This case represents few cases of spinal meningeal cysts in VHL. VHL is most common hereditary kidney disease characterized by cyst formation in the kidneys and other organs. In the nervous system, arachnoid cysts have been found in ~8% of patients with VHL. They are usually asymptomatic, but variable nerve root or spinal cord compression may be present. Low-back pain, radiculopathy, and headache due to cerebrospinal fluid leakage may also occur, thus, such symptoms in a patient with PKD should warrant further investigation for this condition.

Pub171
Perineural Cysts in Poly cystic Kidney Disease
Kanu R. Amari, Jennifer A. Tuazon. Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease characterized by cyst formation in the kidneys and other organs. In the nervous system, arachnoid cysts have been found in ~8% of patients with ADPKD. These cysts can compress the spinal cord, resulting in pain, paresthesia, and motor weakness.

Case Description: A 51 y/o man presented to the Nephrology clinic for ADPKD. He underwent an MRI of the abdomen to calculate his total kidney volume. Incidentally he was found to have multiple T2 hyperintense lesions in the intercostal space suggestive of perineurial cysts in the left paraspinal paraspinalic thoracic spine. A dedicated MRI of the thoracic spine was subsequently performed which further characterized the lesions to reflect perineural cysts.

Discussion: Perineural cysts are benign pouches filled with cerebrospinal fluid (CSF) located at the nerve root canals along the spine. Only a few cases of spinal meningeal cysts/perineural cysts have been reported in association with ADPKD. Most cases are asymptomatic, but variable nerve root or spinal cord compression may be present. Lower back pain, radiculopathy, and headache due to cerebrospinal fluid leakage may also occur, thus, such symptoms in a patient with ADPKD should warrant further investigation for this condition.
PUB173

A Male Senior with Alport Syndrome in Digenic Inheritance of COL4A3 and 4A4
Shinichiro Koga, Section for Nephrology and Hypertension, Department of Medicine, Tokyo Metropolitan Police Hospital, Tokyo, Japan.

Introduction: Alport syndrome (AS) sometimes show positive in alpha 2 (α2(IV)) and 5 (α5(IV)) chains of type IV collagen in the glomerular basement membrane (GBM). This could illustrate with the facts that: 1) α5(IV) in basement membranes of Bowman corpus and cortex are normally immunofluorescent in 20 % of autosomal recessive AS (ARAS) patient 1); and 2) autosomal dominant AS (ADAS) as well as normal kidney are known to be positive in α5(IV).

Case Description: A 21-year-old Asian male senior (“the patient”) was referred to nephrology outpatient clinic due to persistent microscopic hematuria for over fifteen years. No apparent kidney abnormality was found in echogram so was observed till fourth grade of elementary school. Not only himself but his mother and elder brother had hematuria; this brother recently had complained of low-tone hearing loss. The patient had no ocular defect nor hearing loss; no hypertension, diabetes, nor hypercholesterolemia. Serum Cr 0.95 mg/dl; urine RBC 30-100/HPF, beta2-MG 42 microg/L, and UP/Cr 47.9 mg/gCr. LM of the kidney was near normal. The routine IF examination for lgs and complement components were negative. α2(IV) and α5(IV) were not lack in immunofluorescence staining. EM show 10% area of GBM had irregular thinning; No EDD in glomeruli. SPEEDI-KID version 3.0 2) next generation sequencing covered thoroughly 99.2 % genes, as well as COL4A3, 4A4, 4A5, and 4A6 genes. A known c.G469C;p.G157R 3) and a known c.T4793G;p.L1598R 4) mutation was detected in COL4A3 gene. Novel c.G929A;p.R310Q was detected in COL4A4 gene. No mutation in 4A5 and 4A6 genes. The diagnosis of AS was made of persistent microscopic hematuria, type IV collagen gene mutations, and family history of nephritis. His mother also had a known D682G mutation in COL4A4 3), as well as a known G157R mutation in COL4A3 3). His elder brother has not been investigated so far.


PUB174

A Rare Case of Gordon’s Syndrome

Introduction: Pseudohypoaldosteronism type II (PHAII) or Gordon’s Syndrome, is a rare inherited form of hypertension. It is characterized by hyperkalemia, metabolic acidosis, normal GFR, and a low renin state 2. The main symptoms are polyuria, polydipsia, and hypertension. Hyperkalemia recurred despite an improved SCr of 0.9. Genetic testing revealed a variant c.G469C,p.G157R as well as sodium citrate in patient with improvement in hyperkalemia. Upon follow-up, hyperkalemia recurred despite an improved SCr of 0.9. Genetic testing revealed a variant in the WNK4 gene consistent with Gordon’s Syndrome. The patient was started on 12.5 mg of hydrochlorothiazide and has missed all follow-up appointments to date.

Discussion: The discovery of this rare, inherited disorder has lead to the understanding of potassium and sodium handling along the distal convoluted tubule (DCT) 3. The main disturbance involved is the activation of the thiazide-sensitive NaCl cotransporter (NCC) at the DCT 4. Mutations in WNK1 and WNK4 genes were found to further increase the activity of the NCC as well as decrease surface expression of ROMK 4. There are also findings that a chloride shunt is present 3. It is with these studies that we have been able to identify the causation of pathogenesis and subsequent treatment. Our patient presents as a unique case as this autosomal dominant mutation was found later in life as well as being normotensive which can be present in ~20% of cases 4. Regardless of presentation, one must consider this rare disorder as treatment can be lifesaving.
Acidosis (dRTA) After Switching from Standard of Care to ADV7103
Improvement in Metabolic Control in Patients with Distal Renal Tubular Acidosis (dRTA)

**Methods:** Multiple market research studies were conducted to better understand metabolic control burden across subtypes. All studies were physician-reported. Copies of medical charts or genetic test reports were not provided for verification purposes.

**Results:** Across all studies, respondents reported a large subset of PH patients with moderate to severe renal disease. Specifically, the percentage of patients in CKD Stage 3 or worse was the following: — PH1: 87% (Study 1), 56% (Study 2), and 39% (Study 3) — PH2: 92% (Study 1), 68% (Study 2), and 55% (Study 3) — PH3: 83% (Study 1), 41% (Study 2), and 48% (Study 3). Stone burden was similar across PH subtypes: a urinary excretion of 3.24 (PH1), 3.92 (PH2), and 4.95 (PH3) stones in the last year (study 3) — 62% (PH1), 71% (PH2), and 61% (PH3) of patients with no renal impairment presented with 3 or more stones in 5 years (study 3).

**Conclusions:** Results from these completed market research studies suggest that severe disease burden and progression is consistently reported across PH1, PH2, and PH3.

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**PUB177**

**A Curious Case of Isolated Glucosuria**

**Introduction:** Glucosuria exceeding 25 mg/dL is pathological and is known as frank glucosuria. Glucosuria can be grouped into two categories: defective absorption of glucose and overflow glucosuria. Conditions such as hyperthyroidism, pregnancy, fever, and exercise tend to decrease the renal threshold for glucose thereby resulting in glucosuria. Here we present a case of persistent isolated glucosuria likely due to primary renal glucosuria in a healthy 52-year-old female in the absence of any secondary etiology.

**Case Description:** A 52-year-old female was evaluated for incidental finding of glucosuria. She was a healthy individual with no history of diabetes mellitus or gestational diabetes, dysuria, polyuria or polydipsia, chronic kidney disease or kidney stones. Home medications included simvastatin, trazodone and a combined OCP. Hemoglobin A1c was mildly elevated at 5.9 with glucose of 121. Dipstick urinalysis showed pH of 5.5, specific gravity of 1.008 with trace glucosuria. In our workup, we were not able to identify any specific cause for our patient’s glucosuria. Her HgbA1c was in the prediabetes range however multiple random blood glucose readings were normal. Based on the available information, we suspect that she might have rare genetic mutation in SLC5A2 gene responsible for her glucosuria.

**Discussion:** Glucosuria in a non-diabetic patient is rarely observed in the general population. Primary renal glucosuria (PRG) is an autosomal dominant condition caused by a mutation in the SLC5A2 gene. A defect in this transporter disrupts the kidney normal function of maintaining glucose homeostasis. Based on a few case reports, PRG has not been associated with any renal dysfunction however polyuria, enuresis and later a mild growth and pubertal maturation on long term follow ups has been reported. In rare cases, episodic dehydration and ketosis during pregnancy and starvation have been reported. Few case reports have also linked isolated glucosuria to autoimmune diseases like Graves and undifferentiated connective tissue disease. Our case highlights the importance of monitoring isolated glucosuria in the general population. Majority of the patients presenting with glucosuria also have concomitant diabetes mellitus or chronic kidney disease, however glucosuria in the absence of comorbid conditions is a rare phenomenon which warrants further evaluation and close monitoring for worsening kidney function.

**Methods:**

1. **Commercial Support - Advicenne Pharmaceuticals**
2. **Government Support - Non-U.S.**
3. **Funding:** Government Support - Non-U.S.
Proteinuria or hematuria on urinalysis. Family history was very significant and included bilaterally (8.3 cm and 7.9 cm on right and left respectively) and lack of significant serum creatinine 1.8 mg/dL presented for evaluation. Workup revealed small kidneys genetic testing to help define the etiology of renal disease guided by a relevant family has been shown to poorly predict ADTKD-UMOD. As such, our case highlights the need for considering a rare and often underrecognized diagnosis and in fact, clinical features have been shown to poorly predict ADTKD-UMOD. As such, our case highlights the need for genetic testing to confirm the diagnosis.

**Introduction:** Alport Syndrome is a rare disease among children and adults. The diagnosis is a clinical challenge for adult nephrologists. We illustrate a case demonstrating the use of genetic testing to confirm the diagnosis.

**Case Description:** The patient is a 23-year-old woman who presented with proteinuria and hematuria (serum creatinine 1.8 mg/dL). The patient endorsed a family history of End Stage Kidney Disease (ESKD) in her mother, and in her sister, a complete serum work-up and renal ultrasonography were negative. Kidney biopsy was performed, which showed Focal Segmental Glomerular Sclerosis (FSGS) with diffuse foot process effacement. The patient was started on steroids and lisinopril. After 6 months, the patient did not improve. Genetic testing for Alport Syndrome was positive for the COL4A4 mutation, confirming a diagnosis of autosomal Alport Syndrome despite a lack of classic symptoms.

**Discussion:** Alport Syndrome affects one in every 5000 to 10000 adult Americans and causes 0.2% of all ESKD cases in the United States. The pathophysiology involves a targeted screening program of high-risk individuals who remained and did not have evidence of GLA testing were considered to have a screening gap of 1,364 individuals of which 932 were still alive those, 1,386 remained after applying exclusion criteria. Only 22 of 1,386 (1.6%) had high-risk conditions, including, where appropriate, diabetes, hypertension, cardiomyopathy, ischemic stroke <45 years of age, kidney failure or proteinuria of cardiomyopathy, ischemic stroke <45 years of age, kidney failure or proteinuria of unknown cause, peripheral neuropathy. We excluded patients with known contributing factors to these high-risk conditions, including, where appropriate, diabetes, hypertension, autoimmune diseases, cancer, glomerulonephritis, and polycystic kidney disease. Those who remained and di not have evidence of GLA testing were considered to have a 0.5-4.0% probability of having Fabry disease.

**Results:** A total of 145,466 individuals had at least one high-risk condition. Of those, 1,386 remained after applying exclusion criteria. Only 22 of 1,386 (1.6%) had GLA testing, leaving a screening gap of 1,364 individuals of which 932 were still alive and residing in Manitoba as of December 31, 2018. We estimated that screening these individuals would yield between 4 and 37 new cases of Fabry disease.

**Conclusions:** Administrative health databases may be a useful tool to identify patients at higher risk of Fabry disease or other rare diseases. Further directions include designing a program to screen these individuals for Fabry disease.

**PUB182**

**Genetic Testing to Help Navigate the Spectrum of Type IV Collagen Nephropathy**

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**Introduction:** Single gene mutations as an attributable cause of chronic kidney disease (CKD) are becoming increasingly elucidated. Those specifically recognized as being quite impactful involve type IV collagen. While these have been classically associated with Alport’s syndrome, advances in genetics have permitted further understanding of the role type IV collagen plays in the pathogenesis of other causes of CKD.

**Case Description:** 33 year old male with past medical history of excess BMI, and hypertension presented after routine UA displayed proteinuria and hematuria (serum creatinine 1.8 mg/dL). 24 hour study revealed proteinuria of 1.9 g per day and several repeat UAs had ongoing proteinuria and blood/RBC. Family history was significant for the patient’s brother and father both with microhematuria. Kidney biopsy showed focal segmental & sclerosing glomerulopathy, perihilar variant (mild) with glomerulomegaly, diffuse G BM thinning (mean 230 nm) and rare GBM lamellations, most consistent with collagen IV nephropathy. Genetic testing revealed heterozygosity for a pathogenic deletion involving the COL4A4 gene, which is associated with both autosomal dominant and autosomal recessive Alport’s syndrome.

**Conclusion:** Thin basement membrane nephropathy (TBMN) is an entity within the spectrum of genetic hematuria syndromes which historically was considerated to be a benign hereditary condition characterized by thin basement membranes and microscopic hematuria without significant proteinuria or progressive kidney disease. Recent evidence and understanding of type IV collagen mutations has shown that the prognosis of TBMN may not always be so benign. In fact, 29% of patients have been diagnosed with COL4A3/4 develop CKD and 15% progress to ESRD. Phenotypes can be rather variable.
along this genetic continuum and where TBMN specifically fits remains an area of ongoing discussion. Our case utilized genetic testing to confirm a deletion in the COL4A4 gene, after kidney biopsy findings were consistent with collagen IV nephropathy. The associated peripheral variant of FSGS and glomerulomegaly could be considered a risk factor for escalated CKD progression.

**PUB183**

MAGED2 Mutation with Barter’s Syndrome in Adult Patients

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**Introduction:** MAGED2 mutation is associated with a transient antenatal form of Barter’s syndrome that can be severe enough to lead to death.

**Case Description:** 43-year-old woman with a history of pituitary adenoma on cабergoline and levotyroxine, referred to nephrology for hypokalemia, hypocalcemia and hypomagnesemia dependent on replacement therapies, frequent lower extremity muscles cramping and weakness post exercise, with frequent ER visits for vomiting and hypokalemia. A diagnosis of Barter versus Gitelman’s syndrome was raised. Her Blood pressure on average is 90 systolic (80-100, asymptomatic). She noticed worsening LSE, edema and systolic up to 110 lately. Renin and aldol were elevated (36 and 51 respectively). FeNa was 0.03%, FeK of 6.76% and FeCa of 0.1%. The low urinary calcium (3mg/dl) was pointing towards a Gitelman’s syndrome. MRI of the abdomen showed possible liver hemangiomata, simple cyst of the left kidney and otherwise normal kidneys. As a kid, the patient had a constant craving for salt, had muscle cramping while sleeping, had lower extremity edema especially after puberty, and when she was 20 she would have a 9 lbs fluctuation in her weight in one day. Patient’s mother had a pregnancy complicated by polyhydramnios and gave birth to a sister who suffered from nephrocalcinosis and died soon after birth. The patient has a daughter with an avid need to eat salt. She was started on spironolactone and enalapril which improved her edema, blood pressure and resolved the need for potassium. She remained on magnesium, calcitriol and calcium carbonate. Her recurrent vomiting improved after decreasing cabergoline. A genetic panel was ordered and revealed a X-linked MAGED2 heterozygous mutation, normally defined as variant of uncertain significance [P268L and c>T in exon 4]

**Discussion:** MAGED2 is linked to a transient form of antenatal Barter’s syndrome including nephrocalcinosis and symptoms resolve by 1.5 years of age. The mutation present in this patient however, is not described previously and is the first mutation of MAGED2 to cause a Barter’s syndrome that remains pathogenic at an adult age. This might be due to the fact that MAGED2 was described in relation to Barter’s syndrome in 2016 and the focus is on a pediatric population. Learning points: MAGED2 mutation can have a variable phenotype within the same family. MAGED2 mutation can cause Barter’s syndrome that is not limited to the perinatal period.

**PUB184**

Renal-Limited Thrombotic Microangiopathy in the Setting of Thrombomodulin Mutation

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**Introduction:** Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative microangiopathic hemolytic anemia, and organ damage. Common causes of primary TMA are STEC-mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. AKI secondary to TMA in severe Hypertension is not an uncommon scenario, however it is important to rule out primary TMA as a cause of Hypertension. Our case involves a very young male, who presented with elevated Creatinine and severe Hypertension, whose renal biopsy showed renal-limited TMA, with subsequent genetic panel showing Thrombomodulin mutation.

**Case Description:** This is a 29 year old African ancestry male with known history of Hypertension, diagnosed 1 year ago, not on any antihypertensive medication. Patient presented to the ED with chest pain with BP of 230/110 mm Hg. Blood work remarkable for serum Creatinine of 4.9, unknown baseline, K of 3 and serum bicarbonate of 27. Urinalysis remarkable for sterile pyuria with WBC of 100 and UPCR of 1.5 g/g. Patient was admitted under the impression of hypertensive emergency. All the work up for secondary Hypertension, including PRA/serum Aldosterone and Renal Doppler were negative. Serology work up for glomerulopathy including ANA, ANCA, Anti Cardiolipin Ab, Anti GBM Ab, HIV, Hepatitis, Anti PLA2R Ab, C3/C4 were negative. Renal function has not improved despite hypertension management, and renal biopsy was performed, which showed findings suggestive of severe TMA. Haptoglobin and LDH were not suggestive of presence of severe TMA, Hemoglobin level and Platelet counts were never low. Genetic panel for aHUS was sent, which showed THBD mutation, for which Ravalluzumab was initiated, with the plan of 3 to 6 months treatment with close monitoring of renal function. **Discussion:** Though most patients with TMA will present with the hematologic abnormalities of MAHA and thrombocytopenia, there are some that never demonstrate those features and only present with acute renal injury and Renal-Limited TMA. High degree of suspicion of underlying dysregulation of alternative pathway of complement is required, especially if patients do not improve with standard supportive care. Some of those mutations could present with Renal-Limited TMA without features of systemic TMA.
We present a case of a 65 years-old man with history of diabetes mellitus for 6 years without retinopathy, HTN and chronic kidney disease (CKD) who been associated with monoclonal gammopathy, autoimmune diseases and viral infections. The patient with advanced chronic kidney disease is debatable but knowing the diagnosis of we should treat with immunosuppression or continue conservative management in this uncommon to blame HTN as the cause of the CKD. However, diseases such as FGN patients with worsening proteinuria and kidney function even without active sediment seen. Large membrane deposits with segmental mild increase in mesangial cellularity, polyclonal immunohistochemical staining for DNAJB9 was positive, supporting the diagnosis of Primary membranous nephropathy is considered to involve a humoral autoimmune response to a normal podocyte antigen, in the absence of known secondary etiologies including autoimmune diseases, infections, malignancies and certain drugs.

Case Description: We present a case of a 65 years-old man with history of diabetes mellitus for 6 years without retinopathy, HTN and chronic kidney disease (CKD) who presented to our hospital with acute kidney injury after increasing dose of lisinopril for uncontrolled hypertension. Physical exam was unremarkable except for high BP 154/85 mmHg, and mild lower extremity edema. Laboratory studies revealed a serum creatinine of 4.13 mg/dL (baseline 2.9 mg/dL, eGFR 22 ml/min/m²), UPCR of 7.1 g/dL, UA showed 7+ protein. No RBC on repeat UA. He was negative for Hepatitis B, C, and ANCA, anti-GBM, ANA, and anti-dsDNA Ab. C3,C4 were normal, SPEP showed no M spike, and elevated kappa/lambda ratio of 1.81 (89.7 / 49.6 mg/L). Renal biopsy revealed 20-30% interstitial fibrosis, diffuse, moderate to severe mesangial expansion by eosinophilic deposits with segmental mild increase in mesangial cellularity, polyclonal IgG-dominant smudgy mesangial staining with capillary loop expansion with kappa/lambda light chain shift, and mesangial and subendothelial deposits with non-branishing randomly arranged fibrils (7-21 nm). A Congo red stain was negative for amyloidosis. Immunohistochemical staining for DNAJB9 was positive, supporting the diagnosis of FGN.

Discussion: This case highlights the importance of pursuing a kidney biopsy in patients with worsening proteinuria and kidney function even without active sediment and negative work up for GN. In patients with long standing history of HTN, it is not uncommon to blame HTN as the cause of the CKD. However, diseases such as FGN although rare should always be considered as part of our differential diagnosis. Whether we should treat with immunosuppression or continue conservative management in this patient with advanced chronic kidney disease is debatable but knowing the diagnosis of FGN will certainly help to establish a better prognosis.

Negatively, PLA2R-Ab is markedly elevated (PLA2R IFA positive with titer of 1:500 and PLA2R ELISA positive at 250.00 RU/mL). The patient refused to undergo a biopsy. In the absence of a biopsy, a mutual decision is made to treat the patient with rituximab. However, after two doses of rituximab 1g spaced two weeks apart, the patient fails to achieve clinical or biochemical remission within 6 months. The need for a biopsy is again discussed to further determine treatment options, and is eventually done. Biopsy suggests features of secondary MN, including mesangial expansion, intracapillary leucocytes on light microscopy (LM), IgG (1 and 3) and IgM, C3 and C1q deposits, absent PLA2R stain on immunofluorescence (IF), and subepithelial, intramembranous as well as subendothelial electron dense deposits on electron microscopy (EM). Through assessment for secondary causes of MN remains unremarkable. A CT head/chest, chest, abdomen, and pelvis is also obtained which does not reveal any malignancy.

Discussion: Although the biopsy findings are suggestive of a secondary MN, the significance of high titer of PLA2R-Ab has persisted. The patient is offered an alkylating agent based therapy, but has opted to enroll in an ongoing clinical trial on anti-CD 38 therapy. He remains under surveillance for possible secondary etiologies due to his biopsy findings, while awaiting his response to anti-CD 38 therapy.
pulmonary-renal syndrome with negative serologies including ANCA. Based on most recent results from PEXIVAS trial, plasmapheresis was not considered to be part of the treatment plan and not doing plasmapheresis did not affect outcome.

### PUB191

**A Case Report of ANCA-Negative Vasculitis Presenting with Pauci-Immune Glomerulonephritis**

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**Introduction:** Crescentic glomerulonephritis (GN) is a severe form of GN characterized by a rapid decline in kidney function. Pauci-immune GN is one of the most common causes of rapidly progressive GN and is usually associated with positive antineutrophil cytoplasmic antibody (ANCA). We present a rare case of ANCA negative pauci-immune GN that was successfully treated with immunosuppression.

**Case Description:** A 17-year-old girl without significant PMH was admitted to the hospital with abdominal pain and diarrhea. She initially had dark colored urine but became anuric shortly thereafter. On admission, she had a blood pressure of 139/83 mmHg (98 percentile), Pulse of 87 bpm and Temp of 98.3 °F. Physical exam was unremarkable. Initial laboratory investigation revealed creatinine of 11.9 mg/dl. Urinalysis was positive for proteinuria and hematuria. Protein to creatinine ratio was 28 g/g. Urine microscopy showed RBCs with dysmorphic features. ANA, ANCA and anti GBM antibodies were negative. C3 and C4 were normal. Viral serology was negative. Kidney biopsy was consistent with small vessel vasculitis with pauci-immune necrotizing GN. She has initially required dialysis for several sessions but her kidney function improved after we started her on steroids and cyclophosphamide with subsequent improvement of her condition.

**Discussion:** Pauci-immune crescentic glomerulonephritis is one of the most common causes of rapidly progressive glomerulonephritis. The majority of patients with pauci-immune had circulating ANCA. Some patients with pauci-immune crescentic glomerulonephritis lack ANCA.

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**PUB192**

**Atypical Presentation of Anti GBM Disease in an Elderly Woman with No Hematuria and Subnephrotic Proteinuria**

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**Introduction:** Atypical anti GBM disease forms a small minority of patients in this rare and aggressive condition. Atypical disease usually presents with milder disease and typical histopathology and good prognosis. However, presentation without hematuria is unusual.

**Case Description:** A 69-year-old lady with a background history of hyperlipidemia, hypertrophic and rheumatoid arthritis presented with a 4-week history of nausea and lethargy. She had been initiated on Pantaprazole and noted to have renal dysfunction with creatinine at 214 µmol/L 4 weeks later. She had no respiratory symptoms. Urine protein/creatinine ratio was elevated at 108 mg/mmol and she had leukocyturia and no hematuria. The vasculitic screen revealed positive anti GBM titre at 135 CU (QuantaFlash chemiluminescence assay; normal range <20CU). A renal biopsy revealed necrotising glomerulonephritis and distinctive linear IgG deposition on glomerular basement membrane. She underwent daily plasma exchange for one week and subsequently initiated on alternate daily exchanges. She was initiated on pulse Methylprednisolone 500 mg daily for three days followed by oral prednisolone 1 mg/Kg and oral cyclophosphamide 2 mg/Kg. Her renal function continues to improve with creatinine at 177 µmol/L.

**Discussion:** The initial presentation was suggestive of interstitial nephritis especially with the drug history. However, the anti GBM serology and the typical histopathological features were consistent with a diagnosis of anti GBM disease resulting in appropriate therapy. Hence the teaching points from this case are that anti GBM disease can present in an atypical manner and absence of hematuria does not rule out an aggressive glomerulonephritis and timely investigation with a renal biopsy and appropriate management can prevent end stage kidney disease.

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**PUB193**

**IgA Nephropathy and Lupus Nephritis: A Subtype or a Separate Entity?**

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**Introduction:** The relationship between IgA nephropathy (IgAN) and lupus nephritis (LN) is controversial, some feeling the 2 can co-exist while others feel that IgAN could be a subtype of LN. We present a case of SLE that had features of IgAN kidney biopsy which we treated as lupus nephritis resulting in recovery of renal function.

**Case Description:** A 51 year-old female with undifferentiated connective tissue disease consistent with SLE was evaluated for AKI, proteinuria with protein to creatinine ratio of 5.76 grams, and microscopic hematuria. Lab investigation showed negative ANA, c-ANCA, PLA2R Ab, DNA Ab, anti-GBM with normal C3 and slightly high C4. Around this time she was noted to have GI ulcers on scope. Kidney biopsy was performed and sample was sent to Arkana lab. It showed 22 total glomeruli of which were globally sclerosed, no segmental sclerosis or arteriolar hyalinosis, mild interstitial fibrosis and tubular atrophy, severe arterial intimal fibrosis, negative congo red stain for amyloid, and 1 glomerulus on toluidine blue stained sections. LM had crescents in 7/14 glomeruli. IF had 1/7 glomeruli that were globally sclerotic. There was 3+ amounts of mesangial deposits of IgA. 3+ amounts of lambda light chain and 2+ amounts of kappa light chain were seen in a similar pattern. Kappa and lambda light chains stained equally in small casts and in tubulointerstitial regions. EM showed mild effacement of foot processes. The mesangium was not expanded and there were a moderate number of mesangial electron-dense deposits. Pathology reported this as IgA-Crescentic glomerulonephritis and stressed that though an unusual pattern, it was consistent with diffuse class IV lupus nephritis. We treated her with Euro-lupus protocol using glucocorticoid and cyclophosphamide with good recovery of renal function.

**Discussion:** LN is a known complication of SLE and it normally has distinct characteristics on kidney biopsy. IgG deposits are commonly seen on IF in LN but IgA deposits are uncommon. Secondary forms of IgAN can present in patients who have mucosal infections or ulcerations which may have contributed to IgA deposition in our patient. Currently we do not have criteria to precisely differentiate whether these two entities (IgAN and LN) can co-exist. We feel our patient represents a distinct subtype of LN based on clinical history, biopsy findings and response to treatment.

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**PUB194**

**Hemoptysis in Mixed Cryoglobulinemia**

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**Introduction:** Mixed cryoglobulinemia(MC) is a small vessel immune complex vasculitis caused by polyclonal cryoglobulin deposition in major end organs. Pathogenesis has been associated with viruses including hepatitis C and HIV, plasma cell dyscrasias, and connective tissue diseases. Clinical presentation varies but pulmonary manifestations are generally rare. We present a unique case of mixed cryoglobulinemia presenting with kidney, skin and lung involvement.

**Case Description:** A fifty-seven-year old female with a history of alcoholic cirrhosis, chronic kidney disease, diastolic heart failure was initially found to have a petechial rash during admission for syncope at an outside hospital. Her lab workup noted progressive acute kidney injury, cryoglobulin consisting of IgG kappa, polyclonal IgG and IgM lambda, low complement levels, positive rheumatoid factor, and negative HIV, hepatitis C, and ANCA. Skin biopsy revealed leukocytoclastic vasculitis. Kidney biopsy showed proliferative glomerulonephritis with necrotizing arteriolitis. She was treated with intravenous solamedrol for MC but developed hemoptysis followed by acute hypoxemic respiratory failure. Bronchoscopy with bronchialveolar lavage(BAL) revealed thin bloody secretions in the right upper and middle lobe of the lung. Culture and gram stain
noted methicillin sensitive staph aureus(MSSA). Patient was given rituximab, antibiotics and was transferred to a tertiary center for further evaluation and management of plasmapheresis. Bone marrow biopsy was negative for evidence of clonal plasma cell disorder.

Discussion: Pulmonary disease in MC includes cough, dyspnea, and rarely hemoptysis. Hemoptysis from diffuse alveolar hemorrhage (DAH) is documented as a clinical feature of cryoglobulinemia with an estimated incidence of 0.4–4%. We report a case of mixed cryoglobulinemia with persistent hemoptysis despite antibiotics. No sequential BAL done to investigate DAH. MSSA pneumonia noted on BAL is likely a complication of immunosuppression with intravenous steroids. Our case is a valuable addition to the few cases of hemoptysis in MC described in the literature.

PUB195
Management of Infective Endocarditis-Related Glomerulonephritis
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Introduction: Antibiotics can be effective and curative if infective endocarditis (IE) infection is mild. However, in severe cases of IE, surgical intervention is necessary to restore integrity of heart value and to halt or cure IE related glomerulonephritis (GN).

Case Description: 28-year-old male with Cushing’s disease, hepatitis C virus (HCV) infection (viral load >10,000,000 IU/ml), admitted at an outside hospital (8/10–9/15) with creatinine (Cr) 4.2 mg/dL (baseline Cr 1.53 mg/dL) and persistent proteinuria. HCV treatment was initiated. By undergoing liver biopsy, histopathological examination revealed cryoglobulinemia. Hepatitis C treatment.

Outpatient follow up, 3 months later, he was on Coreg only with blood pressure (120/80 mmHg), diuretics, and he was on HCV treatment. At the time of his last visit, he had no evidence of cryoglobulinemia. He had resolution of his proteinuria and stable renal function. By undergoing aortic valve repair rather than replacement of TV not only resulted in lower operative mortality but also improved his renal function.

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PUB197
Urinary GADD45G Protein Excretion Predicts IgA Nephropathy Progression
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Background: Growth arrest and DNA damage 45G (GADD45G) is a family of proteins involved in DNA damage response and cell growth arrest. In the present study, we showed evidence that urinary GADD45G protein can predict progression of IgA nephropathy (IgAN).

Methods: IgAN patients were included in the study if they did not have acute kidney injury on the day of sample collection and had at least one follow up serum creatinine (Scr) measurement after renal biopsy. A 50% or greater increase of serum creatinine levels was used as an endpoint of deterioration of renal function. ELISA assay was performed using a Human GADD45G ELISA kit. Renal biopsy tissue was stained with a monoclonal mouse anti-GADD45G antibody.

Results: Forty-five patients were enrolled in this study whose renal biopsy revealed IgAN. Urinary GADD45G and urinary protein concentrations were 1.89±0.12 µg/g and 1.47±0.18 g/g, respectively. Urinary GADD45G showed a significant positive correlation with SCR-slopes and with urinary protein. The SCR-slope of the highest tertile group (above 1.95 µg/g) of urinary GADD45G was significantly higher than that of the lowest tertile group (below 0.90 µg/g). Proteinuria was significantly higher in the highest tertile group compared to the other tertile groups. Univariate Cox regression analysis showed that urinary GADD45G was significantly associated with deterioration of renal function. Kaplan-Meier test showed a significant difference in event-free survival for deterioration of renal function between patients with the highest urinary GADD45G tertile vs. the other tertile groups. The area under the receiver operating characteristics (ROC) curve indicated urinary GADD45G had a good performance in predicting renal outcome. The cut-off point of 1.67 µg/g was determined from the ROC curve. This cut-off point yielded a positive predictive value of 36.8% and a negative predictive value of 100%. Immunohistochemistry showed that GADD45G was expressed in all biopsy samples of IgAN whereas no staining was noted in normal control tissue. Staining was mainly detected in the cytoplasm of renal tubules.

Conclusions: In the present study, we showed that urinary GADD45G excretion is significantly associated with kidney disease progression in patients with IgAN.

PUB198
Expanding the Differential: Goodpasture’s Disease in the Setting of the COVID-19 Pandemic
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Introduction: The 2020 COVID-19 pandemic was a challenging time in healthcare. Physicians struggled with limited resources, overwhelming patient volume and limited knowledge of COVID-19. During this period many hypoxemic patients with pulmonary infiltrates were empirically managed as COVID-19 patients. However, anchoring to COVID-19 diagnosis narrows differentials and potentially lead to missed diagnosis. Herein we highlight a case of delayed Goodpasture’s disease in the setting of COVID-19 pandemic.

Case Description: A 51 year old male was admitted for several days of malaise, diarrhea and decreased oral intake. On arrival the patient was hypothermic 88.6 °F, BP 122/67 mm Hg, Hgb 10.7, low CO2 25 mm Hg, WBC 17.1 dL, platelets 30,000 µL, albumin 0.9 gm/dL, and low C3 level. Urimaalysis with hematina and proteinuria suggested failure to control the infection as seen by worsening renal function. Kaplan-Meier test showed a significant difference in event-free survival for deterioration of renal function between patients with the highest urinary GADD45G tertile vs. the other tertile groups. The area under the receiver operating characteristics (ROC) curve indicated urinary GADD45G had a good performance in predicting renal outcome. The cut-off point of 1.67 µg/g was determined from the ROC curve. This cut-off point yielded a positive predictive value of 36.8% and a negative predictive value of 100%. Immunohistochemistry showed that GADD45G was expressed in all biopsy samples of IgAN whereas no staining was noted in normal control tissue. Staining was mainly detected in the cytoplasm of renal tubules.

Conclusions: In the present study, we showed that urinary GADD45G excretion is significantly associated with kidney disease progression in patients with IgAN.
The Alteration of Neutrophil Nuclear Morphology: A Potential Predictor for Corticosteroid Response in IgA Nephropathy
Reiko Muto, Sawako Kato, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: In patients with active IgA nephropathy (IgAN), immunosuppressive treatment using corticosteroid is widely used. It should be useful to detect a poor corticosteroid responder in advance. Neutrophils are the most abundant white blood cells (WBC) in circulation, representing a first line of defense from daily environmental insults. Recently, there have been reported associations between an alteration of neutrophil nuclear morphology and treatment responses in patients with infection, cancer, and autoimmune diseases. In these states, the neutrophil nuclear breaks down, then the nucleosome components extrude. The aim of study is whether an alteration of neutrophil nuclear morphology associates with poor corticosteroid response in IgAN.

Methods: We investigated IgAN patients starting corticosteroid therapy between July 2020 to March 2021. We excluded patients with apparent infection or cancer. We defined the alteration of neutrophil nuclear morphology as neutrophil blebs (NB) with Giemsa stain (Figure 1). The participants with NB greater than the median NB were grouped in the high-NB group and the rest were in the low-NB group.

Results: We enrolled five biopsy-proven IgAN patients; number of female, 4; median age, 51 [interquartile range (IQR): 41-57] years old; median WBC count, 7700 [IQR: 6100-9550] /µL; median eGFR, 58.5 [IQR: 56-69] ml/min/1.73m²; median CRP, 0.06 [IQR: 0.01-0.64] mg/dL; median UP, 0.7 [IQR: 0.2-1.4] µg/µL; median NB, 53.2 [IQR: 37.6-69.2] % at baseline. The high-NB group showed the significantly decrease in UP than that low-NB group after 4 weeks from the initiation of corticosteroid therapy (p=0.0516). There was no differences in eGFR.

Conclusions: The alteration of neutrophil nuclear morphology could predict the response to corticosteroid therapy in IgAN patients.

PUB201
Nile Red Fluorescence and Spectroscopy Reveal Unique Lipid Droplet Distribution and Physicochemical Changes in Glomerulonephritis
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Background: Abnormalities in lipid deposition and lipid droplet (LD) accumulation have not been well established in glomerulonephritis (GN). Nile Red (NR), a well-known lipophilic fluorophore, is a solvatochromic fluorophore that provides high-resolution spatial assessment of lipid distribution and chemistry. Solvatochromatic spectroscopy is a sensitive imaging modality with the potential to characterize the subtle, early changes in lipid chemistry associated with glomerular injury and disease.

Methods: A total of 72 kidney biopsies of histologically diagnosed glomerular diseases including minimal change disease, membranous nephropathy, primary FSGS, class IV lupus nephritis (LN), ANCA-associated vasculitis, and IgA nephropathy (IgAN), and healthy tissue controls were retrieved from the Biobank for the Molecular Classification of Kidney Disease. Quantitative spectral analysis of NR emission patterns were performed on NR-stained biopsies to generate unique physicochemical profiles for each type of GN. Segmented regions of biopsies (glomeruli, tubules, and interstitial) were imaged using confocal microscopy allowing for LD quantitation using an algorithm developed in MATLAB.

Results: Lipid droplet distribution greatly differed between the GN with IgAN and LN demonstrating the highest number LDs in glomeruli. By spectral analyses, control tissue showed significant differences in lipid polarity profile between histological compartments of the kidney (glomeruli, interstitium and tubules). Tubules consistently displayed more lipid rich domains compared to interstitial and glomerular regions. In diseased states, these patterns varied between GNs, with glomerular regions becoming more polar (for example in LN) and tubular regions (predominantly for IgAN). Within histologically identical disease types, we noted distinct populations based on lipid profiles, suggesting significant variance within GN.

Conclusions: Nile Red spectral analysis of human kidney tissue provides unique insights into lipid physicochemical changes in GN. Marked variance within identical disease types suggests that histological determinants of GNs are limited and sensitive techniques such as high-resolution imaging and spectroscopy can identify earlier changes in disease.

PUB202
ANCA Vasculitis: Detecting It Early
Kiran Patel, Joe N. Austin. The Christ Hospital Physicians Spine, Cincinnati, OH.

Introduction: Renal limited vasculitis (RLV) is part of the spectrum of antineutrophil cytoplasmic autoantibody (ANCA) vasculitis and includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). GPA and MPA present with kidney and pulmonary involvement. RLV tend to present later in the disease course given the lack of extrarenal symptoms that are seen with GPA and MPA. They can progress into having GPA and MPA with development of extrarenal manifestations. Here we present a case in which renal limited vasculitis is diagnosed early in its course.

Case Description: 54 year Hispanic male with no medical history was admitted with atrial fibrillation, acute heart failure, hyperthyroidism and melena. Patient had no history of recurrent sinus or respiratory infections. On exam, patient had a saddle nose deformity from an accident as a child and lower extremity edema. Creatinine (Cr) was 0.54 on admit and was also 0.54 in the emergency room one week prior. Uremia had large blood with >100 RBC/HPF and 30mg/dL protein. Patient was diuresed aggressively for 3 days with a furosemide drip and with a mild bump in creatinine from 0.73 to 1.16. The patient’s renal function deteriorated even after losartan and furosemide were discontinued and nephrology was consulted when Cr was 2.23. Evaluation showed ongoing microscopic hematuria. Serologic studies were ordered and renal biopsy was performed. Biopsy showed pauci-immune necrotizing glomerulonephritis (GN) with crescents. C3 and C4 were low and C-ANCA and anti-proteinase 3 were strongly positive.

Renal limited vasculitis therapy with Solumedrol followed by weekly rituximab x 4 doses, renal function continued to decline. Due to aggressive clinical course, he was started on plasma exchange x 7 treatments. Despite interventions, he became oligo-anuric and required initiation of dialysis. Although he has had some recovery of renal function and is no longer oligo-anuric, he remains dialysis-dependent.

Discussion: Renal limited vasculitis is confirmed by kidney biopsy, and commonly shows necrotizing GN with crescents in the early stages. As the disease progresses, the lesions become more sclerotic. Untreated glomerulonephritis can progress to end stage renal disease within weeks. Treatment requires pulse methylprednisolone with 500 to 1000mg/day for three days followed by oral prednisone along with cyclophosphamide or rituximab. In rapidly decline in Cr continues, plasmapheresis is warranted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Unanticipated Severe Thrombocytopenia Linked to Mixed C- and P-ANCA-Positive Vasculitis

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Introduction: The Anti-Neutrophil Cytoplasmic Autoantibody (ANCA)-associated vasculitis are a rare group of disorders that affect multiple organ systems with a peak age of 65-74 years. It encompasses several diseases including Granulomatosis with polyangiitis, Microscopic polyangiitis and Eosinophilic granulomatosis with polyangiitis. Few cases have been able to demonstrate the existence of mixed ANCA vasculitis related to severe refractory thrombocytopenia.

Case Description: We report a 74-year-old male with Past Medical History of Hypertension (Stage-IV), Chronic Kidney Disease (CKD) Stage IV that came to our hospital complaining of fatigue and decrease urinary output since 5 days. Physical exam was remarkable for bilateral crackles and lower extremity edema. Initial labs showed evidence of anemia and thrombocytopenia of 5.8 g/dl and 66 10^3/µL respectively. Multiple electronic records review showed history of prior injury over CKD. serum creatinine 7.25 mg/dl (baseline: 3.85), marked azotemia BUN:101 mg/dL and metabolic acidosis: 13 mEq/L. Patient was admitted with diagnosis of volume overload to start emergent renal replacement therapy along with PRBC transfusion. Follow up labs revealed evidence of hemoglobin optimization (10.2 g/dl), improved azotemia (65 mg/dl) and metabolic acidosis (19.3 mEq/L). Further work-up sent by nephrology service showed evidence of high levels of Proteinase 3 ANCA antibodies: 4.9 U/ml and Myeloperoxidase ANCA antibodies: 96.4 U/ml. Decision was made to start induction therapy with Rituximab and high dose pulse IV steroids. Despite aggressive treatment, clinical course continued to deteriorate with thrombocytopenia reaching critical values of 19 10^3/µL. Other causes in the differential diagnosis were rule out such as Thrombocytopenia Purpura, Chronic lymphocytic leukaemia, HIV, Hepatitis C, Thrombotic thrombocytopenia purpura, among others, which indicated an association between mixed ANCA vasculitis and severe refractory thrombocytopenia.

Discussion: This case illustrates a routinely found inpatient lab abnormality not generally seen in this rare vasculitis type. It is important to keep a wide-ranging differential diagnosis in patients presenting with refractory thrombocytopenia concomitant to advance renal failure. Prompt identification and suspicion of ANCA vasculitis can lead to early start of induction therapy which can delay the progression to end stage kidney disease.

A 32-year-old Caucasian male with PMH of uncontrolled HTN, chronic microscopic hematuria, and anemia presented with hypertensive emergency (BP171/94 mmHg) and acute myeloid leukemia (BUN: 58 mg/dL & SCR: 4.41 mg/dL). UA showed microscopic hematuria and proteinuria. 24-hr urine protein was 8.5 g/24h. Renal US was unrevealing. Other studies were negative including autoimmune panel, SPEP, UPEP, C3/C4, serum FLC, anti-PLA2R, anti-TSHD7A, illicit drug screen, anti-neutrophil cytoplasmic autoantibodies, and anti-Chlamydia (both IgG and IgM), infectious (hepatitis panel, HIV, antiretroviral therapy). A kidney biopsy showed a membranoproliferative pattern with cellular/ fibrinolytic cellular crescents, 15% interstitial fibrosis, predominant lambda IgG3 and C3 granular capillary loop staining, and numerous subendothelial, mesangial and subepithelial deposits on EM. A bone marrow biopsy showed hypocellular marrow trilaminar hemagglutination. No clonal cells were identified. He was started on prednisone 80 mg x 4 weeks. Renal function deteriorated and so he was treated with Rituximab (4 doses, 375 mg/m2/dose; briefly interrupted by COVID-19 infection). Absolute CD20 count 4 weeks after this treatment showed 1 cell/ml with no improvement in renal function or proteinuria.

Discussion: PGNMID is challenging to treat due to its rarity, and here we highlight a case without detectable clone or monoclonal protein in serum/urine that failed prior published effective treatment strategies. The reconstitution of CD20 after treatment completion may suggest that a stronger dose or treatment is necessary to achieve clinical response. Daratumumab (a monoclonal anti-CD38 antibody) was recently studied in an open-label phase 2 study to treat 11 PGNMID patients, and this is our next step. Our case highlights the evolving treatment modalities of PGNMID.

Atypical Haemolytic Uremic Syndrome in Lung Transplantation and Treatment with Eculizumab: Our Experience

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Background: Atypical haemolytic uraemic syndrome (aHUS) is a clinical entity characterized by acute kidney injury, thrombocytopenia and microangiopathic hemolytic anemia. There are several cases of AHUS in non-secret solid organ transplants described in the literature, included lung transplant. Kidney and patient survival are compromised by this complication because of the lack of an effective treatment. Eculizumab, a C5 complement factor specific blocker already administered in another kind of secondary aHUS with encouraging results.

Methods: We analyse six lung transplants in a retrospective single-center study between 2018-2020 who developed an aHUS and were treated with eculizumab. Clinical and analytical data were collected along the follow-up. Principal outcome was to explore haematological and renal response after treatment with eculizumab.

Results: We included a total of six patients (83% female) with a median age of 57 years at transplantation and a median follow-up of 12 months (range 6-36). Four patients developed an aHUS 5 months (33-95) after transplantation. Previously, a bronchoscopic procedure lead to early onset proteinuria in a patient with history of SLE. Goal of treatment is to produce haematological and renal response after treatment with eculizumab.

Conclusions: aHUS is a critical complication in lung transplantation, shortly after transplantation reaching hypocomplementemia. We included a total of six patients (83% female) with a median age of 57 years at transplantation and a median follow-up of 12 months (range 6-36). Four patients developed an aHUS 5 months (33-95) after transplantation. Previously, a bronchoscopic procedure lead to early onset proteinuria in a patient with history of SLE. Goal of treatment is to produce haematological and renal response after treatment with eculizumab.
Double Positive Glomerulonephritis: A Disease Associated with Unfavourable Outcome Requiring Aggressive Treatment: A Case Report and Review of Literature

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Introduction: Co-presentation with both ANCA and anti-GBM Ab is not unusual and associated with worst outcome (Tab.1); the prevalence of double-positivity in Good-Pasture Syndrome (GPS) is higher (30-38%) than in ANCA-associated vasculitis (AAV) (5-14%).

Case Description: A 70-year-old woman was admitted with a severe respiratory distress and AKI (stage 3) requiring urgent dialysis. Laboratory tests revealed high titer of ANCA (MPO >134 IU/ml, PR3 20 IU/ml) and anti-GBM Ab (54 IU/ml). Histopathological renal analysis showed chronic lesions (Fig. 1). Steroids, plasma-exchange and Rituximab were therefore administered. A sensible improvement of titer of ANCA (MPO >134 IU/ml, PR3 20 IU/ml) and anti-GBM Ab (54 IU/ml).

Discussion: Double-positive patients show hybrid features: the acute phase, similarly to GPS, is characterized by frequent lung hemorrhage, warranting plasma-exchange sessions; the subacute phase, like AA V, by high rate of recurrence, requiring a more intense and prolonged maintenance immunosuppressive regimen. Renal biopsy represents a useful diagnostic tool to establish chronicity degree and to speculate about pathogenetic contribution of each component. The worst renal outcome and higher risk of relapse require a careful follow-up.

A Rare Case of Severe AKI from Fibrillary Glomerulonephritis Harshul Desai. The University of Texas Health Science Center at Houston John P and Katherine G McGovern Medical School, Houston, TX.

Introduction: Fibrillary glomerulonephritis (GN) is an uncommon disorder found on less than 1 percent of native kidney biopsies done worldwide. Due to its rare prevalence, the association of this disorder with other diseases is not fully understood. Here we present a case of a 60-year-old woman with a history of hypertension and untreated Hepatitis C who presented with acute oliguric kidney injury and was subsequently found to have biopsy proven fibrillary GN.

Case Description: 60-year-old woman with history of hypertension and Hepatitis C presented with shortness breath and back pains. Labs on admission showed an elevation in BUN and Cr to 121 mg/dL and 7.09 mg/dL respectively. Other findings included an elevated globulin gap of 4.6 g/dL and a urine dipstick with minimal proteinuria. Renal ultrasound was negative for obstruction and showed normal sized kidneys. Serum and urine protein electrophoresis with immunofixation revealed the presence of free monoclonal lambda light chains. Beta-2 microglobulin level was elevated to 12.4 mg/L. These clinical and laboratory findings raised suspicion for light chain cast nephropathy secondary to multiple myeloma and so renal and bone marrow biopsies were performed. Bone marrow biopsy showed no abnormal plasma cell clones, suggesting against a diagnosis of multiple myeloma. Furthermore, no lytic lesions were noted on skeletal survey. Renal biopsy showed findings consistent with fibrillary GN as well as acute pyelonephritis even though patient experienced no symptoms of urinary tract infection during the entirety of the hospitalization. She was started on intravenous antibiotics, and her renal function returned to near normal on day 14 of hospital stay. She was discharged home with appropriate Nephrology and Oncology follow up.

Discussion: Fibrillary GN is a poorly understood cause of renal failure. Treatment of the disorder is based on the underlying cause if one can be found. Approximately 30-50% of cases are associated with a hematological malignancy, autoimmune disease, monoclonal gammopathy, or Hepatitis C infection. For our patient, the renal biopsy failed to show monoclonal immunoglobulin deposits, suggesting that the most likely condition was the underlying Hepatitis C. Also, the finding of acute pyelonephritis on the biopsy likely indicates an entirely separate (though still possibly related) disease process which probably also contributed to the renal injury.

A Case of TAFRO Syndrome with Two Consecutive Renal Biopsies Following the Pathological Course of the Kidney Noritoshi Kato,1 Tomonori Hasegawa,2 Reiko Muto,1 Akihito Tanaka,1 Yoko Sato,3 Kayaho Maeda,1 Kazuhiro Furuhashi,1 Shoji Saito,1 Tomoki Kosugi,1 Shoichi Maruyama.1 1Nagoya University Graduate School of Medicine, Nagoya, Japan; 2Handa City Hospital, Nagoya, Japan.

Introduction: Renal involvement of TAFRO syndrome consists of diffuse glomerular endothelial injury. But due to thrombocytopenia and deterioration of general condition, there are few reports on kidney biopsy results. We report a rare case of TAFRO syndrome with two consecutive renal biopsy which shows pathological time course of endothelial injury from acute to chronic phase.

Case Description: A 20-year-old female who presented with high fever, pleural effusion, ascites, thrombocytopenia, lymph node enlargement, and proteinuria around 1.0g/day. First, she was diagnosed as systemic lupus erythematosus and treated with prednisolone. But she showed poor response to the therapy. Then she was transferred to our hospital and received renal biopsy for definite diagnosis. The renal specimen showed no evidence of immune complex nephritis, but showed diffuse global swelling of endothelium and expansion of subendothelial space. TAFRO syndrome was diagnosed based on 3 major and 2 minor criteria. She was treated with oral prednisolone and tocilizumab, and once CRP titer became negative. But 3 weeks after first tocilizumab treatment, her CT images revealed worsening of ascites, lymph node swelling. CRP titer again became positive, and massive proteinuria appeared. We considered the situation as relapse of the disease and reduced the interval of tocilizumab doses. A second renal biopsy was performed two months after the first one to investigate the cause of the large amount of proteinuria. Interstitial fibrosis was observed in 15% of renal cortex. Glomeruli showed global collapse or focal segmental double contour. One glomerulus showed mesangiolysis and endocapillary hypercellularity. No thrombosis was observed on TAF stains, and partial loss of CD31 staining was confirmed in a damaged glomerulus. Owing to the enhanced treatment, she achieved remission for one year.
Discussion: The pathological course of renal damage associated with TAFRO syndrome is very rapid. This subset of patients usually presents clinically differently with distinct histopathological features. Long-term follow-up in these patients is also needed to study the natural history of C5-inhibitor (eculizumab) in refractory cases of lupus nephritis (r-LN) and refractory ANCA-associated glomerulonephritis (r-AGN).

Methods: In this retrospective study, nine consecutive patients were included (r-LN: n=3 and r-AGN: n=6). All patients were previously treated with three or more drugs: corticosteroids (n=9), mycophenolate (n=9), rituximab (n=5), immunoglobulin (n=5), therapeutic plasma exchange (n=4), cyclophosphamide (n=1), and belimumab (n=1). Eculizumab was considered for use in off-label indication in patients with progressive renal deterioration (worsening creatinine, protein-to-creatinine ratio) or developing a high-risk lethal complication after the induction immunosuppressive therapy. The histologic lesson observed were: a) r-LN: Type VI (n=1), Type V (n=1), and type IV (n=1), and b) r-AGN: sclerotic (n=3), and malignant hypertension (+/-) thrombotic microangiopathy (n=1), in two patients who developed pulmonary haemorrhage, no renal biopsy was performed.

Results: Mean age (SD): 54 (17) years. Median (min-max) of follow-up: 23 (24,8) months. Overall, 2(22%) patients are in chronic renal replacement program (one r-AGN patient who was dialysis dependent at presentation, and presented a complement H mutation, and one r-LN within 12 months after the onset eculizumab). 8 patients showed hypertension. As a whole the mean (95%CI) eGFR (EPI-CMD) increased: 8.0 (-3.0 to 19.1) ml/min/1.73m² (P = 0.13). In r-LN, the mean (95%CI) eGFR increased: 13 (-1.8 to 28.25), P = 0.07; while in r-LN, a slight change was observed: -2.1 (24.8 to 20.59), P = 0.72. The median (25-75 percentile) protein-to-creatinine ratio decreased from 2.6 (1.6-5.5) to 0.60 (4.1-12) mg/mg (P = 0.01). The eculizumab doses [median (25-75 percentile)] required in r-LN and RAG patients were: 8400 (7800-10200) mg and 3150 (2475-5700) mg, respectively. No major side effects were recorded.

Conclusions: The coadjuvant complement inhibition with eculizumab stabilized or improved renal function and decelerated the vascular complications. The short course of eculizumab seems to be highly effective in r-AGN, and also was associated with lower doses needed.

Lupus Nephritis Presenting with Positive PR3-ANCA and Decreased ADAMTS13

Mujahed Abuailouf, Roberto L. Collazo-Maldonado. Methodist Dallas Medical Center, Dallas, TX.

Introduction: Lupus nephritis is a well-described entity. The simultaneous presence of ANCA abs is rare and is related to poor prognosis. Positive patients usually have MPO-ANCA. We present a case of biopsy-proven Class IV/V Lupus nephritis with PR3-ANCA and decreased ADAMTS13 activity in an AA man.

Case Description: This 46-year-old AA man with no known past medical history presented to the ED for two weeks of SOB, leg, and scrotal swelling. He denies any associated symptoms. He denies using any other OTC medications and illegal drugs. On exam, vital signs were stable. He had 2+ pitting edema in LE bilaterally, scrotal and penile edema. Other systems were unremarkable. Labs were significant for Hg 5.1, Platelets 106, K 6.9, CO2 9, BUN 78, Cr 10.2, and Albumin 2.4. UA showed dysmorphic RBCs and proteinuria, and Urine protein/creatinine ratio of 9. COVID-19 testing was negative.

Discussion: The patient later underwent therapy with CyBorD whereafter his swelling improved. A normal serum Cr of 0.89. SPEP followed by serum immunofixation showed an M-spike which was difficult to quantitate. Kappa to lambda ratio was low at 0.06. Extensive work up to determine the etiology for nephrotic syndrome was performed which was followed by a kidney biopsy, showing lambda light chain deposition on immunofluorescence and positive birefringence of Congo red stained material under polarized light. Electron microscopy showed haphazardly arranged fibrils and foot process effacement. Consistent with amyloid deposition and nephrotic syndrome respectively. An echocardiogram, skeletal survey and PET scan obtained to exclude any other organ involvement, were insignificant. Patient was referred to hematology-oncology and he underwent a bone marrow biopsy which showed 10-20% involvement by a plasma cell neoplasm. With the information gathered, the diagnosis of AL amyloidosis with multiple myeloma was made.

Discussion: Monoclonal gammopathy is defined by presence of a monoclonal immunoglobulin in plasma, urine or both produced by clonal plasma cells. It could be associated with hematologic malignancy, smoldering, MGUS or a relatively new term monoclonal gammapathy of renal significance. We present a case of monoclonal gammapathy associated with renal damage leading to the diagnosis of multiple myeloma.

A Case of Biopsy Proven Kidney Restricted AL Amyloidosis Leading to Diagnosis of Multiple Myeloma

Ruta Shah, Alexander PENNEKAMP, John Hergenrother. The Christ Hospital Physicians Spine, Cincinnati, OH.

Introduction: Monoclonal gammapathy is defined by presence of a monoclonal immunoglobulin in plasma, urine or both produced by clonal plasma cells. It could be associated with hematologic malignancy, smoldering, MGUS or a relatively new term monoclonal gammapathy of renal significance. We present a case of monoclonal gammapathy associated with renal damage leading to the diagnosis of multiple myeloma.

Case Description: A 69 year old male with history significant for hypertension, CAD, PVD presented to the office with bilateral lower extremity swelling extending up to his trunk and significant weight gain over the past month. Laboratory investigations revealed serum albumin of 2.6g/dl, cholesterol 300mg/dl, LDL 187mg/dl. Urine analysis revealed macroalbuminuria with a urinary protein-to-creatinine ratio of 14.31mg/g in the setting of a normal serum Cr of 0.89. SPEP followed by serum immunofixation showed an M-spike which was difficult to quantitate. Kappa to lambda ratio was low at 0.06. Extensive work up to determine the etiology for nephrotic syndrome was performed which was followed by a kidney biopsy, showing lambda light chain deposition on immunofluorescence and positive birefringence of Congo red stained material under polarized light. Electron microscopy showed haphazardly arranged fibrils and foot process effacement, consistent with amyloid deposition and nephrotic syndrome respectively. An echocardiogram, skeletal survey and PET scan obtained to exclude any other organ involvement, were insignificant. Patient was referred to hematology-oncology and he underwent a bone marrow biopsy which showed 10-20% involvement by a plasma cell neoplasm. With the information gathered, the diagnosis of AL amyloidosis with multiple myeloma was made. The patient later underwent therapy with CyBorD whereafter his swelling improved.

Discussion: An unimpressive SPEP should not be ignored. In the setting of high clinical suspicion, work up should always be followed by kidney and bone marrow biopsy. About 12-15% of patients with renal AL amyloidosis have associated multiple myeloma which require treatment with chemotherapeutic agents. Even though our patient fits into the monoclonal gammapathy associated with hematologic malignancy, MGUS is an evolving topic which deserves considerable attention because many of these entities benefit from clonal based therapies.
Hematuria and Proteinuria in a Patient of Cypriot Descent

Kelly V. Liang,1 Brigid K. Ellis,2 Michael B. Stokes,3 Richard J. Smith,3 Daniel P. Gale,4 University of Pittsburgh, Pittsburgh, PA; 2Tower Health, Reading, PA; 3The University of Iowa Hospitals and Clinics Department of Pathology, Iowa City, IA; 4University College London, London, United Kingdom; 5Columbia University Irving Medical Center, New York, NY.

Introduction: C3 glomerulonephritis (CGSN) caused by a mutation in complement Factor H-related protein 5 (CFHR5) is endemic in patients of Cypriot descent. CFHR5 nephropathy bears a striking resemblance to IgA nephropathy (IgAN). We present a case of CFHR5 nephropathy in a Cypriot patient who was initially diagnosed with IgAN and highlight the importance of family history, labs, renal biopsy, and genetic testing in diagnosis of CFHR5 nephropathy.

Case Description: A 22-year-old male of Cypriot and Greek descent presented in June 2019 with recurrent microscopic hematuria and proteinuria. Due to slowly progressive renal dysfunction, a renal biopsy was performed in January 2020, which showed mild mesangial hypercellularity, segmental duplication of basement membranes, and glomerular C3 deposits. Immunofluorescence was negative for IgG, IgM, C1q, light chains, or fibrin. Electron microscopy revealed segmented mesangial, subepithelial, and subendothelial immune-type electron dense deposits with segmental duplication of glomerular basement membranes. He was diagnosed with CGSN. Genetic testing confirmed the CFHR5-CFHR5 fusion gene that has been causally linked to CGSN by a gain-of-function effect leading to overactivation of the alternative complement pathway. He was treated conservatively with Lisonpril 10 mg daily. Home blood pressure remains stable. SCr remains 1.5 to 1.9 mg/dL and UPCR remains 610 to 810 mg/g Cr.

Discussion: CFHR5 nephropathy is endemic in patients of Cypriot descent. Therefore, a high index of suspicion for CFHR5 nephropathy should be maintained in Cypriot patients presenting with nephritic syndrome. The presentation of CFHR5 nephropathy bears a striking similarity to IgAN. The main distinguishing features of CFHR5 nephropathy vs. IgAN are its familial nature and absence of IgA deposition. Therefore, family history, renal biopsy, and genetic testing for CFHR5 mutation are critical in establishing a diagnosis of CFHR5 nephropathy.

Benralizumab Monotherapy Substitution Therapy in Symptomatic Asthma Exacerbations of Eosinophilic Granulomatosis with Polyangiitis

Macaulay A. Onuigbo,1 University of Vermont College of Medicine, Burlington, VT.

Introduction: There is increasing interest in the use of the biologicals including anti-interleukin 5 and anti-interleukin 5 receptor antibodies in the management of steroid-resistant or steroid-dependent eosinophilic granulomatosis with polyangiitis (EGPA). Benralizumab, an anti-IL 5 receptor antibody is steroid sparing. We describe successful substitution Benralizumab monotherapy in EGPA.

Case Description: In late 2005, a 38-year old male was diagnosed with multisystemic disease. He presented with recurrent fever, joint pain, rash, dyspnea, peripheral eosinophilia, Eosinophil count (Figure 2) after its introduction in April 2019. He was treated with antibiotics and 73.3% underwent IS. All developed kidney dysfunction (median SCr 6.1mg/dL), 60% needing RRT. In hospital mortality was 20%. At discharge 26.7% remained RRT-dependent and 46.7% had AKD; only one patient presented total recovery. At 3mo of follow-up (n=12), one new patient had total recovery, 33.3% remained RRT-dependent and 66.7% had median eGFR 40.0mL/min. At 12mo (n=11) one patient died (unrelated cause); 36.3% remained with CKD, 36.3% maintained RRT and 27.3% maintained recovery. Data related outcomes regarding IS and IgA dominance showed that neither influence recovery. During follow-up a new episode of infection was detected in 50% of cases, most of them with AKI associated.

Conclusions: Overall IRGN had poor kidney outcome and it seems that treatment with IS did not improve that, although it is important to highlight that all patients IS-treated had more severe disease. Patients with IgA-dominant IRGN had better eGFR. Our results correspond to a small series of a single centre; therefore, future research is needed to better understand risk factors for outcomes.

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positive with a negative C1q pointing towards alternate and/or mannose-binding lectin complement pathway activity.

**PUB219**

**Diabetic Nephropathy: A Great Mimicker or Mistaken Identity**

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**Introduction:** Monoclonal gammapathy of renal significance (MGRS) is often a challenging diagnosis due to wide spectrum of disease and difficulty in establishing a pathogenic link between monoclonal proteins and kidney disease. Here, we describe a biopsy ‘proven’ diabetic kidney disease in a non-diabetic patient, diagnosed as membranoproliferative glomerulonephritis (MPGN) years later with robust clinical response to treatment.

**Case Description:** A 68-year-old male with stage 3A-B CKD, hypertension and monoclonal gammapathy of uncertain significance (MGUS) was referred to renal clinic for second opinion on biopsy ‘proven’ diabetic kidney disease in 2013 despite never being a diabetic. A repeat kidney biopsy in 2020 for persistent proteinuria revealed MPGN with segmental subendothelial electron dense deposits (Figure 1). Unfortunately, IF was inconclusive due to inadequate sample. After ruling out other etiologies, he was treated as MGRS with velcade and dexamethasone with excellent clinical response with improvement in renal function and resolution of proteinuria (Figure 2).

**Discussion:** This case brings up an interesting clinical question: could the original diagnosis of diabetic nephropathy be early changes related to MGRS and was it a mistaken identity? Serial kidney biopsies are rarely done in MGRS but could provide guidance as illustrated by our experience.

**PUB220**

**AKI Associated with Anticoagulant-Related Nephropathy in a Newly Diagnosed IgA Nephropathy**

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**Introduction:** Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that may be caused by anticoagulation with warfarin and other anticoagulants. It is an underestimated cause of AKI with poor renal prognosis. AKI is probably resulting from glomerular hemorrhage and the characteristic pathologic findings consist of obstruction of renal tubules by red blood cell casts, which do not contain Tamm-Horsfall protein.

**Case Description:** A 58-year-old Caucasian man presented with AKI stage 3 (serum creatinine 5.9mg/dL) complaining of macroscopic hematuria. Two months ago, he underwent aortic valve replacement with a mechanical valve and he began taking acenocoumarol as an anticoagulant agent (serum creatinine 0.9mg/dL). He also presented INR 2.2, several dysmorphic erythrocytes in urine sediment and 24-h urinary protein excretion 5g/day. The renal biopsy revealed mild mesangial hypercellularity, acute tubular necrosis with occlusive red blood cell casts and interstitial inflammation. The immunoflorescence presented mild mesangial deposits of IgA (2+) and C3 (1+).

We consider that the cause of AKI was anticoagulant-related nephropathy rather than IgA nephropathy because there was no history of prior infection and the presence of numerous RBC tubular casts could not be explained just by these glomerular findings taking acenocoumarol as an anticoagulant agent (serum creatinine 0.9mg/dL). He also presented INR 2.2, several dysmorphic erythrocytes in urine sediment and 24-h urinary protein excretion 5g/day. The renal biopsy revealed mild mesangial hypercellularity, acute tubular necrosis with occlusive red blood cell casts and interstitial inflammation. The immunoflorescence presented mild mesangial deposits of IgA (2+) and C3 (1+)

Due to the severe interstitial nephritis, pos prednisolone 1mg/Kg/daily was added to his treatment, with a gradual reduction in 4 months and acenocoumarol was replaced by tinzaparin. After 1year renal function remains stable at creatinine level 2.5mg/dL, proteinuria <1gr/24h, without microscopic hematuria. Considering the poor renal prognosis, it highlights the necessity for close vigilance of renal function, as well as, urine sediment in patients, who begin on anticoagulation, especially with pre-existing renal diseases, including glomerulopathies and those with glomerular hyperfiltration.

**PUB221**

**Eculizumab for Treatment of Recurrent Pregnancy-Triggered Atypical Hemolytic-Uremic Syndrome with a Mutation in Complementation 3: A Case Report**

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**Introduction:** In atypical hemolytic-uremic syndrome (aHUS), thrombotic microangiopathy (TMA) often develops due to mutations in complement-related genes or autoantibodies to complement regulators. Anti-C5 monoclonal antibodies (eculizumab and ravulizumab) are expected to improve prognosis. However, the significance of genetic testing is unknown. We report a case of pregnancy-triggered aHUS that was successful with plasmapheresis and eculizumab administration.

**Case Description:** A 37-year-old Japanese female who had a twin pregnancy underwent a scheduled cesarean section at 37 weeks gestation. On the second day after her delivery, she developed thrombocytopenia, hemolytic anemia, and renal dysfunction. TMA was suspected, and plasma exchange (PE) was started on the 3rd day after her delivery, and steroid pulse was started on the 4th day, and then prednisolone 60 mg/day was administered. Since Shiga toxin-producing Escherichia coli in her stool was negative and both ADAMTS13 activity and inhibitor were normal, the patient was clinically stable.

**Figure 1: Electron microscopy with sub-endothelial deposits**

| Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only |
| Underline represents presenting author. |
calcineurin inhibitors may be renal and life saving. In our patient, with a more benign or HLH, multiorgan failure may be life threatening prompting early immunosuppressive associated with MAS in the settings of AD and malignancies. When associated with MAS, multiorgan failure may be life threatening prompting early immunosuppressive treatment. Though rare, HGP is considered in the differentials of acute GN prompting early renal biopsy. If clinical picture is severe, treatment with steroids and calcineurin inhibitors may be renal and life saving. In our patient, with a more benign course of HGP likely due to EBV, clinical improvement was rapid with supportive care alone. Without RB, appropriate treatment for other forms of GN, microangiopathic injury or vasculitis might have been delayed.

Case Description: 52-year-old male with DM, HTN presented(Pre-Pandemic) with 4 days of fever, chills, myalgia with severe joint stiffness and pain. On exam, he had hand swelling and tenderness. Labs noted hemoglobin 11.9, platelet(plt)69000, bicarbonate 26, BUN 47, creatinin(G) 3.4 mg/dl, urinalysis(UA) with >1000 mg protein, 11 red cells and 10 white cells. UA and Cr(0.8) was normal one year prior. Other tests noted a 24 hour urine protein of 4gm, TSat 12%, ferritin 295, ANA(1:320), anti ds-DNA 1-80, elevated EBV and Parvovirus IgM and IgG, positive EBV nuclear antigen, low C3(8-14-44), C4(46-88-165), ESR 64 with negative cryoglobulin, hepatitis B, C, anti-GBM, RF, ANCA, urine immunofixation and serum protein electrophoresis. By day 2 of admission, he became oliguric with urine output(UO)=<500cc/day, CO2 decline to 19 a hyperuricemia. RB demonstrated endocapillary histiocytes, endothelial cell swelling with mild lymphocytic deposits and 80%foot process effacement. With supportive therapy (IV fluids, holding ACE, anagliesis) his arthritis resolved. By day 4, UO increased, Scr improved to 1.5 and plt normalized. Anemia persisted and was treated with IV iron

Discussion: HGP has been reported secondary to acute viral illnesses and may be associated with MAS in the setting of CAD and malignancies. When associated with MAS or HLP, multigorgan failure may be life threatening prompting early immunosuppressive treatment. Though rare, HGP is considered in the differentials of acute GN prompting early renal biopsy. If clinical picture is severe, treatment with steroids and calcineurin inhibitors may be renal and life saving. In our patient, with a more benign course of HGP likely due to EBV, clinical improvement was rapid with supportive care alone. Without RB, appropriate treatment for other forms of GN, microangiopathic injury or vasculitis might have been delayed.

PUB225

Autologous Mesenchymal Stromal Cell Therapy for Idiopathic Nephrotic Syndrome: The MESNEPH Study

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Background: Corticosteroids represent first-line treatment of idiopathic nephrotic syndrome (INS). However, 60-80% of patients present multiple relapses and require steroid-sparing immunosuppression with significant toxicity. New therapeutic approaches with a better safety profile are needed. Mesenchymal stromal cells (MSC) exert immunomodulatory functions, regulating cells of both adaptive and innate immune systems.

Methods: Approximately 20 patients (age-range 5-40 years) with multi-relapsing INS were included. The study will primarily assess the feasibility and safety of this new therapeutic approach in INS patients. The study is ongoing, last patient visit is expected in July 2021.
Safety and Efficacy of Avacopan (CCX168) in a Pediatric Patient with C3 Glomerulopathy

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Introduction: C3 glomerulonephropathy (C3GN) is a subtype of C3 glomerulopathy, characterized by alternative pathway complement activation and intense C3 immunofluorescence on renal biopsy. C5a is a potent pro-inflammatory mediator of the complement system, whose chemotactic effects are mainly mediated by the interaction with complement C5a receptor (C5aR) expressed on the cell surface. Avacopan is an orally administered selective inhibitor of C5aR.

Case Description: An 11-year-old female with biopsy-proven C3GN was initially treated with three intravenous (IV) boluses of methylprednisolone then tapered to oral prednisone (PDN) given with mycophenolate mofetil (MMF) and an angiotensin-converting enzyme inhibitor (ACE-i). Complete remission was achieved, PDN was stopped, and MMF and ACE-i were maintained. Twelve months following remission, due to relapse of proteinuria (urinary protein/creatinine ratio (UPCR) 1.19 mg/mg), a second course of PDN therapy was started and cyclosporin (CyA) was added to the therapy. A high level of C5b9 was found. Since the patient never achieved complete remission, she was enrolled in the ChemoCentryx ACCOLADE study, which was a randomized, double-blind, placebo controlled study. Patients received avacopan or matching placebo for the first 26 weeks, followed by open-label avacopan in all patients for the following 26 weeks. At the end of the open-label phase, her UPCR was 2.09 mg/mg. Following avacopan, a progressive reduction of proteinuria of approximately 0.5 mg/mg was observed. In the last 4 weeks of the study, avacopan was discontinued, and an increase in proteinuria (UPCR 0.7 mg/mg) was observed, which continued to >1 mg/mg in the subsequent weeks. The patient also reported increased fatigue. After about 3 months, authorization for compassionate use of avacopan was obtained and the patient experienced improvement in her physical well-being and a reduction of proteinuria of approximately 0.5 mg/mg. CyA was discontinued, but it was rapidly reintroduced due to a transient increase of proteinuria. In the following months, proteinuria remained low despite the interruption of MMF. At the last follow up (>16 months from open-label start) UPCR was 0.29 mg/mg and the drug was well tolerated.

Discussion: To the best of our knowledge, this is the first report on the use of avacopan in a pediatric case of C3GN.

Rituximab for Steroid-Dependent Minimal Change Disease in Adults

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Introduction: Minimal change disease (MCD) accounts for 15% of adult nephrotic syndrome, out of which 25% have frequently relapsing nephrotic syndrome and 30% become steroid dependent. Here we report four cases of relapsing or steroid dependent MCD in adults who were treated with rituximab and their long term follow up.

Case Description: Retrospective chart review of 4 adult patients with relapsing or steroid dependent minimal change disease treated with rituximab at the University of Virginia with more than 6 months follow up following rituximab infusion.

Discussion: The discussion shows a summary of demographics and laboratory values for these patients. All four patients achieved complete remission and remained steroid free, at least 18 months following treatment with rituximab, although 2 had relapses that responded to another dose of rituximab. One case was treated with immunosuppressive drugs for decades and had developed several complications.

Dapsone-Induced Methemoglobinemia in a Patient with Minimal Change Disease

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Introduction: Dapsone is commonly used as a second line medication in treatment and prevention of pneumocystis pneumonia. Its use has been associated with life-threatening conditions, namely methemoglobinemia.

Case Description: A 34-year-old female presented to Nephrology clinic for evaluation of proteinuria in the setting of weight gain. She had 4 prior pregnancies with one complicated by HELLP and another by preeclampsia. A week prior to presentation, she reported waking up with significant swelling in her face and legs. She had a protein to creatinine ratio of 12 grams/gram of creatinine at her primary care’s office. Her serum albumin was 1.9 gram/deciliter. Her other serological workup was negative or normal. Her hemoglobin A1C was 5.1%. The patient does not take NSAIDs or OTC medications. Her hemoglobin A1C was 5.1%. The patient does not take NSAIDs or OTC medications. A kidney biopsy showed minimal change disease. Prednisone was started at 1mg/Kg along with Atovaquone for PCP prophylaxis. Patient had a prior history of anaphylactic reaction to Bactrim. Given COVID19 pandemic, Pentamidine administration has been restricted due to droplet isolation. Atovaquone was subsequently replaced with Dapsone due to poor palatability. The patient was hospitalized for worsening dyspnea with new oxygen requirement two weeks later. Her oxygen partial pressure at room air was 32 mmHg with a normal A-a gradient. She had lost 10 pounds and was no longer on diuretics. The patient was euovolemic on exam. An echocardiogram was unremarkable. A CTA of the chest to assess was negative for pulmonary edema and pulmonary embolism. The patient had new anemia (hemoglobin was 11.3 from a baseline of 14 g/dL). She did not have signs of hemolytic anemia (LDH, bilirubin, haptoglobin and peripheral smear were normal). Her methemoglobinemia levels were then tested given recent initiation of dapsone. Methemoglobinemia levels were then tested given recent initiation of dapsone and were found to be elevated at 11.5%. Dapsone was consequently discontinued, and she was transitioned back to Atovaquone after taking it with food. Discontinuation of dapsone resulted in significant symptomatic improvement without further need of supplemental oxygen.

Discussion: Methemoglobinemia is a rare but serious adverse event of Dapsone. Methemoglobinemia is a rare but serious adverse event of Dapsone. Teaching points: - Knowledge about options for PCP prophylaxis is essential when using high dose steroids in the treatment of glomerular diseases. - It is important to counsel and monitor patients being started on Dapsone for potential side effects (hemolytic anemia and methemoglobinemia).
Kidney Function in Patients with Lupus Nephritis Followed Up for a Very Long Time
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Background: Most investigations of long-term outcome in patients with lupus nephritis (LN) focus on end-stage kidney disease (ESKD), but seldom on the progression of patients left with chronic kidney disease (CKD). Both CKD and lupus are non-traditional risk factors for cardiovascular morbidity. We therefore looked at the development of CKD in a subset of LN followed for a very long time in an LN clinic.

Methods: A retrospective chart review was conducted in biopsy-proven LN patients followed for at least 10 years in a single-center, multidisciplinary LN clinic. Patients with CKD were defined as having an eGFR <60 mL/min/1.73 m², and those with ESKD as having an eGFR <15 mL/min/1.73 m² or requiring permanent kidney replacement therapy. eGFR was determined by the clinical laboratories the patients used and was race adjusted. Results were analyzed with descriptive statistics.

Results: 72 patients were followed for a median of 17.1 years (range 10 to 38.7) after LN was confirmed by kidney biopsy. The mean (= standard deviation, SD) age at diagnostic biopsy was 31.8±14.1 years. 21 patients were of African ancestry, 4 were Asian, and 47 were White. ESKD developed in 12 patients (16.7%) after a median of 14.6 years. At the time of last follow-up, 27 patients (37.5%) had CKD with a mean (± SD) eGFR of 40.4±13.0 mL/min/1.73 m². Of the 27 patients who developed CKD, 21 experienced at least one episode of eGFR <50 mL/min/1.73 m² that lasted for at least 6 months. Of the other 6 CKD patients, 4 (67%) had at least one 6 month (or longer) episode of proteinuria > 3.5 g/d.

Conclusions: These data suggest that over 50% of LN patients may be at risk for developing ESKD or CKD if followed for 10 or more years. Almost all of these patients had sustained periods of kidney injury resulting in eGFR <50 mL/min/1.73 m², nephrotic-range proteinuria, or both preceding ESKD or CKD. Immunosuppression may not be sufficient to prevent CKD in LN. These patients may benefit from intense anti-progression therapy.

Staphylococcus aureus Infection-Related IgA Vasculitis with Kidney Involvement
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Introduction: IgA Vasculitis (IgAV), a systemic small vessel vasculitis with IgA dominant/co-dominant immune deposits, is characterized by purpura, arthralgias, and kidney involvement. Staphylococcal IgA vasculitis (IgAV-N) patients, including methicillin-resistant Staphylococcus aureus (MRSA), infection with glomerular IgA deposits known as IgA-dominant infection related glomerulonephritis (IgA-IRGN), is a variant of IRGN whose management remains controversial.

Case Description: A 46-year-old White male with diabetes, lumbar discitis with recurrent MRSA bacteremia, and normal kidney function [baseline SCr 0.7 mg/dl] presented with bilateral lower extremity palpable purpura and petchoea, polyarthralgia, diarrhea; without urinary complaints. Concomitant MRSA bacteremia without an adequate source (iatrogenic interoception of lumbar hardware) or evidence of endocarditis was found. Skin biopsy revealed leukocytoclastic vasculitis with direct IF (+) for IgA, C3, and fibrin confirming IgAV. Urinalysis revealed nephritic sediment. Sr albumin was 2.3 g/dl; random UPCR was 3 g/g. Workup including lupus serologies, cryoglobulins, ANCA, Anti-GBM, RF, ASO, Hepatitis B/C, HIV, paraproteinemia testing were negative. Complements were normal. Sr on admission was 0.8 mg/dl; peaked to 1.4 mg/dl on the 3rd hospitalization day likely in setting of contrast-related AKI, multifactorial ATN, and potential IgAV-N secondary to MRSA infection. He was started on IV vancomycin, IV methylprednisolone, IVIG, and dapsone. SCr returned to baseline on 5th day. Total prednisone 60 mg/d with a rapid taper was started. Rash, kidney function, and proteinuria improved; hence a kidney biopsy wasn’t pursued. Blood cultures turned negative; he was discharged on IV daptomycin/cefaroline and prednisone taper X 6 weeks.

Discussion: Kidney histopathological features of IgA-IRGN are similar to those of IgA/NANAV. Correct diagnosis is imperative as IgAN and IgAV-N likely necessitate immunosuppressive (IS) treatment, while initial IS can exacerbate infection in IgA-IRGN. In our patient, skin biopsy clinched diagnosis of IgAV, and was treated with IS given widespread systemic disease, and antibiotics, with rapid improvement of kidney function abating need for kidney biopsy. Individualized approach for the management of IgA-IRGN is therefore warranted.

Treatment Dilemma of Immune Complex Deposition of Unclear Significance in Hypocomplementenic Urticarial Vasculitis Syndrome
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Introduction: Hypocomplementenic urticarial vasculitis syndrome (HUVS) is a rare autoimmune disorder with recurrent urticaria, glomerulonephritis, and arthritis. Literature reports 50% or more of patients with HUVS have renal involvement that can be delayed up to a decade after diagnosis and portends a poorer prognosis. Treatment is aggressive immunosuppression.

Case Description: 36 year old female with HUVS diagnosed July 2020 and anxiety was admitted in April 2021 with HUVS flare and intermittent microscopic hematuria. Rheumatologic and Dermatology followed. Vitals remained stable. Euvolemic with unremarkable exam, no rash. No signs of systemic lupus erythematosus. Creatinine 0.5mg/dl and hemoglobin 8.9mg/dl, at baseline. Urinalysis: moderate blood, RBC >20/hpf, no WBCs, no bacteria. 24 hour urine PCR 0.20. Renal ultrasound unremarkable. Urine sediment negative for dysmorphic RBCs or casts. Negative infectious workup. Glomerulonephritis workup: positive ANA 1:320 speckled, C3 64mg/dL, C4 18mg/dL, beta 2 glycoprotein IgM antibody 73.3 cu. Remanier of workup negative. Renal biopsy with scattered mild glomerular immune complex deposition, mildly thickened arteries but no active disease. Due to unclear significance of renal pathology and patient preference, no further immunosuppression pursued other than hydroxychloroquine with frequent lab monitoring. One month after discharge, HUVS skin manifestations worsened and she was started on mycophenolate mofetil 1000mg BID at the time of writing.

Discussion: There is a high rate of kidney involvement in HUVS. Early HUVS renal involvement can manifest as intermittent microscopic hematuria, such as this case. The patient also had rare immune complex deposition in HUVS. Renal biopsies may capture this early, subclinical disease. This can lead to a treatment dilemma of whether to wait for renal disease progression to become clinically significant or to treat subclinical disease with non-regimented immunosuppressants with the quandary of how to monitor therapy response, such as frequent renal biopsies. Renal biopsy monitoring is not ideal in all patients, especially those with anxiety; therefore, expectant monitoring was pursued. Due to the rarity of the disease, there is no standard treatment for HUVS renal involvement. More research is needed to determine optimal therapies, especially for subclinical disease.
Hypertension Center, Cincinnati, OH
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PUB234

A Case of Malignancy in NELL-1 Membranous Nephropathy
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Introduction: The predominant target antigen for primary membranous nephropathy (MN) has been Phospholipase A2 receptor (PLA2R), which is present in approximately 70% of cases. Neural epidermal growth factor like 1 protein (NELL-1) was recently identified as one of four new antigens in a distinct type of primary MN. NELL-1 membranous nephropathy was found to be the first candidate antigen highly prevalent in malignancy associated MN, seen in nearly 33% of all cases. We will review a case of NELL-1 membranous nephropathy.

Case Description: A 54-year-old Caucasian female presented from her PCP’s office with shortness of breath, left flank/lower back pain, and bilateral lower extremity edema for four days. Physical exam exhibited BP 170/99 mmHg, non-tender cervical lymphadenopathy (LAD), left CVA tenderness, and 2+ pitting edema. Initial lab studies were significant for elevated D-dimer, hyperprothrombinemia (AII 1.7g/dL), and nephrotic range proteinuria (UPCR 13.5g). Imaging revealed bilateral subsegmental pulmonary emboli, a left renal vein thrombosis, and extensive bilateral LAD (axillary, supraclavicular, mediastinal, and left periaortic retroperitoneal). Given concerns for a podocyteopathy due to a possible lymphoma, the patient underwent an unremarkable extensive serologic workup and a renal biopsy. Her biopsy revealed NELL-1 membranous nephropathy, with diffuse (3+) fine granular staining along glomerular capillary loops for NELL-1 and numerous subepithelial deposits with severe foot process effacement. The patient underwent a bone marrow biopsy, excisional right axillary/cervical lymph node biopsies, PET scan, infectious workup, and age-appropriate malignancy screenings, which were all non-diagnostic for a malignancy. Her biopsies showed reactive nephropathy with concern for evolving B-cell lymphoproliferative disorder with plasmacytic differentiation. Given her biopsy findings and high NELL-1 MN, the patient was treated with rituximab.

Discussion: NELL-1 is a rare emerging subtype of MN that has been identified in both primary MN and malignancy associated nephropathy. A thorough malignancy workup is warranted in all patients diagnosed with NELL-1 MN. More research is needed in the association between NELL-1 and specific cancers, in hopes of guiding future treatments for this disease.

PUB235

Vitamin D Status and Its Association with PTH in 73645 Caucasian Outpatients
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Background: 25-hydroxyvitamin D (25(OH)D) inhibits the synthesis of PTH. However, the limited size of clinical studies to date has only allowed a relatively crude analysis of the relationship between 25(OH)D and PTH.

Methods: We investigated this relationship in 73645 patients (Figure 1).

Results: The relationship between 25(OH)D and iPTH has three phases: an initial drop in iPTH (25(OH)D: 0–20 ng/mL); a horizontal phase (25(OH)D: 20–66 ng/mL); a final drop in iPTH (25(OH)D: ≥60 ng/mL). A Cox regression analysis of these three phases considering age, sex, 25(OH)D, calcium, phosphate, and creatinine showed that in the initial phase age (RR: 0.20; CI: 0.09–0.31, p<0.0001), sex (RR: 0.5; CI: 0.4–0.6), and creatinine (RR: 0.75; CI: 0.6–0.9) are relevant. In the second phase age (RR: 0.14; CI: 0.09–0.20, p<0.0001), sex (RR: 0.6; CI: 0.5–0.7), and creatinine (RR: 0.5; CI: 0.4–0.6) are relevant. In the third phase, only sex (RR: 1.5; CI: 1.1–1.9, p<0.0001) and creatinine (RR: 2.0; CI: 1.5–2.6, p<0.0001) play a significant role. Analyzing the relation between iPTH and 1,25-dihydroxyvitamin D (1,25(OH)2D) in a subset of the study (N=2441) revealed that serum 1,25(OH)2D concentrations have no effect on iPTH.

Conclusions: In conclusion, circulating 1,25(OH)2D does not contribute substantially to the regulation of iPTH in healthy subjects. Presumably, serum 25(OH)D that is converted to 1,25(OH)2D after megalin-mediated uptake in the parathyroid chief cells plays the critical role. The relationship between 25(OH)D and iPTH has three phases. Factors correlating independently with PTH in the different phases differ substantially. 25(OH)D is only relevant in the first initial phase.

PUB236

Metabolic Features of Patients Older than 80 Years Receiving Total Parenteral Nutrition (TPN)

Background: Advances in surgical and interventional techniques has extended the use of TPN in patients unable to receive enteral support. Metabolic abnormalities in “elderly” individuals receiving TPN has been reported > 65 yo but few focusing on > 80.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Reduced GFR, low muscle mass, and multiple comorbidities create unique management challenges. Use of a multidisciplinary approach as described may mitigate TPN associated electrolyte derangements and mortality. For this retrospective study we report some of the clinical parameters associated with “extreme” elderly patients receiving TPN.

Methods: A TPN team consisting of a nephrologist/intensivist, abdominal/critical care surgeons, statistician and surgical PA met daily at 1030 to consider all referrals and create orders by 1230 for a TPN specialty pharmacist review followed by administration at 1730. 38 patients between 1/1/2019-12/15/2020 receiving CENTRAL parenteral nutrition (no PPN) were included. Metabolic complications of 1 or more times were reported.

Results: Baseline characteristics of the study male, 55% female Mean Age (range): 86 years (80-98 years) BMI <19 kg/m2: 18% BMI 30-39 kg/m2: 24% Severe Malnutrition: 66% HbA1c >6.5%: 5% GFR <60 mL/min/1.73m2: 34% TPN Characteristics Mean days on TPN (range): 14 days (4-39 days) Mean energy dose: 26.7 kcal/kg/day Mean creatinine clearance <1.7 mg/kg/1.73m2: 26% protein, 50%CH2, 24% lipid Metabolic Complication(\(\text{m} = 38\)) Hyperglycemia (blood glucose >200 mg/dL) 50%(19) Hypoglycemia (blood glucose <60mg/dL)3%(1) Hypertension (blood pressure >140/90 mmHg) 30%(9) Hypokalemia (<3 mEq/L)8%(3) Hyperkalemia (>5 mEq/L)2%(<1) Low potassium (< 3.5 mEq/L) in 1st 2 days on TPN 32%(12) Low phosphorus (< 2.5 mg/dL) in 1st 2 days on TPN 34%(13)

Conclusions: Expected “refeeding” hypo K and PO4 were observed but critical situations <2 and 1.5 respectively and early fatalities not encountered given daily monitoring and aggressive supplementation. Very frequent hyperkalemia largely of the “SIADH Type” was mitigated by fluid restriction and or high osmolar load. Na levels ≤ 125 or >150 were not seen after initiation of TPN. We believe that a concerted multidisciplinary team approach is extremely useful in provision of the high risk “TPN medication”.

Renal Artery Stenosis

PUB239

Epithelial Overexpression of Human ACE2 in Mice as a Model for Studying Renal Disease

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Background: ACE2 is an integral part of the renin angiotensin system (RAS) and is highly expressed at the brush border of epithelial cells of the renal proximal tubule. Within the lumen, ACE2 is poised to metabolize angiotensin II and extinguishing its effects as part of the counter-regulatory arm of the RAS. Use of transgenic mouse models has been essential in exploring the cardiovascular and renal functions of ACE2. Limitations in using mouse models for SARS was overcome by generation of mice expressing human ACE2 (hACE2) downstream of the keratin 18 promoter (K18-hACE2) by McCray et al 2007. K18-hACE2 mice express hACE2 in epithelial cells throughout the body and have proved valuable for the study of SARS-CoV and CoV2 viral infectivity and pathogenesis. Here, we investigate whether K18-hACE2 mice might serve as a unique tool with which to study the role of ACE2 in the intra-renal RAS.

Methods: We assessed ACE2 activity in urine collected from K18-hACE2 mice (obtained from B6 x 129 strain and bred in our own colony) and their wildtype littermates. Urine was collected over 24 hours in individual metabolic cages, and enzymatic activity was determined using an ACE2 activity assay, Duplicate samples tested for each animal.

Results: Our lab has a longstanding interest in the role of ACE2 in the kidney and our preliminary experiments demonstrate that K18-hACE2 mice have significantly increased Ace2 enzymatic activity in the urine compared to wildtype littermates (1597.0±379.74 vs 396.0±379.92, p=0.013).

Conclusions: The increased urinary ACE2 activity suggests that there are elevated levels of ACE2 reaching the kidney. While this seems most likely due to increased expression of renal epithelial ACE2, soluble ACE2 derived elsewhere and able to reach the lumen of the nephron might also be considered. Thus, K18-hACE2 mice with increased urinary ACE2 activity can serve as a model to examine the effect of ACE2 and the RAS on kidney diseases such as hypertension and acute renal injury.

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Nephrotic Syndrome Secondary to Paraneoplastic Syndrome of Leukemia

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Introduction: Paraneoplastic glomerulopathies are rare manifestations of neoplastic disease that must be differentiated from iatrogenic renal injury. Nephrotic Syndrome is one of the most frequent presentations of paraneoplastic glomerulopathies. Such findings might serve to identify prognosis of disease course. It has been reported that solid tumors are associated with membranous nephropathy while lymphomas are associated with minimal change disease. While the incidence of paraneoplastic glomerulonephropathies in Chronic lymphocytic leukemia (CLL) is unknown and rare. CLL is one of the most common type of leukemia in Western countries. It is commonly observed in elderly patients but it is hasn’t been associated with renal glomerulopathies. Recent studies suspected that leukemic cells might have certain properties that lead to the development of nephrotic syndrome.

Case Description: This is the case of a 82 y/o male patient with past medical history of hypertension, hypercholesterolemia, and prostate cancer that presented to the hospital with complaints of edema. Associated symptoms were malaise, poor urinary output and nausea. Physical examination was remarkable for generalized edema with pitting edema +2 on lower extremities. Initial laboratory work up was remarkable for findings of acute renal injury accompanied by oliguria and proteinuria +3. Despite foley placement and diuresis no major improvements on renal function was observed. Due to constant deterioration he was started on hemodialysis with adequate response but further work up for nephrotic syndrome was requested. ANCA and ANA was negative and serum cryoglobulin. Complement such as C3 and C4 were within normal limits. Fat Biopsy was performed. Report was remarkable for changes suggestive of membranous
glomerulonephritis. In addition, due to sudden decrease in hemoglobin levels and elevated light kappa chains bone marrow biopsy was performed. Report was remarkable for changes suggestive of CLL.

Discussion: This case exhibits a patient that did not presented with symptoms or findings suggestive of CLL at the time of renal injury. Therefore, this case strongly underlines the importance of performing a bone marrow biopsy to patients that present with abnormal electrophoresis and immunofixation in order to detect lymphoproliferative disorder. Early detection can help to treat such disease at early stages and avoid further complications that might affect patient’s prognosis.

PUB241
A Case of Immune-Complex-Mediated Glomerulonephritis Associated with Pembrolizumab
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Introduction: Immune checkpoint inhibitors (ICI) are changing the way we treat cancer. However, these agents have various systemic adverse events that may preclude their use and cause poor patient outcomes. ICI-associated acute kidney injury is an emerging complication of this treatment.

Case Description: An 80-year-old man diagnosed with metastatic adenocarcinoma of the lung with high PD-L1 expression was evaluated for new-onset proteinuria and elevation of serum creatinine. The patient had completed four cycles of carboplatin, pemetrexed, and pembrolizumab at the initial evaluation. His only complaint was foamy urine. Vital signs were remarkable for elevated blood pressure. The physical exam was unremarkable. Laboratory data showed serum creatinine of 1.8mg/dl (baseline of 1.18mg/dl, two months prior), blood urea nitrogen of 24mg/dl, and serum albumin of 3.3g/dl. Urinalysis showed proteinuria, and moderate blood with 9 RBC/HPF. A spot urine protein/creatinine ratio of 10.8 g/g. A kidney biopsy was performed, which showed immune complex-mediated glomerulonephritis, with a membranoproliferative and diffuse segmental endocapillary proliferative pattern of glomerular injury.

Discussion: Kidney immune-related adverse events occur in about 2.5% of patients receiving ICI therapy. Recently there has been an increasing recognition of its association with glomerular diseases. Several differential diagnoses were considered that could have instigated these pathological findings. Ultimately, our team had a high clinical suspicion that they were associated with ICI therapy. After a multidisciplinary discussion, the decision was to hold pembrolizumab and start prednisone at a 1mg/kg dose. The patient responded well to therapy, was discharged home with prednisone taper; subsequent protein/creatinine ratio had a striking improvement to 1.8g/g. The serum creatinine was back to baseline. To our knowledge, this is the first case reported of pembrolizumab-associated immune-complex glomerulonephritis. Patients undergoing ICI therapy require close monitoring for potential kidney adverse events. Physicians must remain vigilant and be able to recognize a potential glomerular injury from ICI therapy.

PUB242
Renal Cell Carcinoma Incidentally Discovered in Native Kidney During Imaging for Superior Vena Cava Obstruction
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Introduction: Papillary RCC accounts for approximately 15% of all kidney cancers, and these can be divided into type 1 and type 2 subtypes based on histopathologic features. As with clear cell cancers, papillary RCC originates from the proximal tubule, but these tumours are morphologically and genetically distinct malignancies. The initial information on their molecular pathogenesis was derived from cases arising in patients with hereditary forms of RCC.

Case Description: A 37-year-old male patient with recurrent FSGS post renal transplantation currently on dialysis has been diagnosed with myeloproliferative disorder. A kidney biopsy was performed which revealed an acute TMA with findings of myocarditis on cardiac MRI. He was found to have AKI with creatinine elevation of 1.15mg/dl and albuminuria of 510 with Urine sodium of 59 was consistent with the diagnosis of the syndrome of inappropriate antidiuretic hormone release (SIADH). Further workup included 8.00 AM cortisol of 0.5 mcg/dl increasing up to 9.3 mcg/dl in two hours after Cosyntropin 250 mcg IV stimulation along with inappropriately normal levels of ACTH of 18.4 pg/ml suggestive of secondary adrenal insufficiency. Additionally, relatively low TSH (with low free T4) along with low LH were suggestive of pituitary insufficiency. FSH and prolactin were within normal range. MRI brain was without any evidence for pituitary adenoma.

Discussion: This case is an excellent illustration that hyponatremia in the patients receiving checkpoint inhibitors could be from hypothyroidism. Extensive work up to detect pituitary insufficiency should be considered in such cases as hypothyroidism could present as the initial sign of pituitary insufficiency.

PUB243
Immune Checkpoint Inhibitor (ICI)-Associated Hypopituitarism Presenting as Severe Hyponatremia
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Introduction: ICI has improved the prognosis for patients with advanced malignant disease. However, as their use increases, it is important to be aware of their potential side effects that require prompt attention. Here, we report a case that presents with life-threatening severe hyponatremia from secondary adrenal insufficiency as the first sign of hypopituitarism secondary to ICI therapy.

Case Description: A 67-year-old man with a past medical history significant for metastatic clear cell type renal cell carcinoma, status post radical right nephrectomy, and adrenalectomy. He was found to have a metastatic lesion to his lungs and was initially treated with Pembrolizumab along with Axitinib for almost one year. 5 months later, He was found to have a metastatic necrotic mass in the right renal fossa and was started ipilimumab/nivolumab x 4 cycles followed by maintenance monthly nivolumab. Almost 4 months after being initiated on ICI therapy and almost 3 weeks after the last dose, labs showed severe hyponatremia with serum sodium of 115 mmol/L with serum osmolality of 249 mmol/L. Clinical examination was suggestive of euvolemic. Urine osmolality of 510 with Urine sodium of 59 was consistent with the diagnosis of the syndrome of inappropriate antidiuretic hormone release (SIADH). Further workup included 8.00 AM cortisol of 0.5 mcg/dl increasing up to 9.3 mcg/dl in two hours after Cosyntropin 250 mcg IV stimulation along with inappropriately normal levels of ACTH of 18.4 pg/ml suggestive of secondary adrenal insufficiency. Additionally, relatively low TSH (with low free T4) along with low LH were suggestive of pituitary insufficiency. FSH and prolactin were within normal range. MRI brain was without any evidence for pituitary adenoma. The patient was treated with the addition of hydrocortisone and levodroxythione. Follow-up labs at one month showed serum sodium of 132 mcg/dl.

Discussion: This case exhibits a patient that did not presented with symptoms or findings suggestive of CLL at the time of renal injury. Therefore, this case strongly underlines the importance of performing a bone marrow biopsy to patients that present with abnormal electrophoresis and immunofixation in order to detect lymphoproliferative disorder. Early detection can help to treat such disease at early stages and avoid further complications that might affect patient’s prognosis.
focal glomerular capillary thrombosis, multifocal arteriolar thrombosis, and arteriolar fibrinoid necrosis (Figures 1, 2). The patient was started on imatinib with improvement of creatinine to 1.75 mg/dL.

Discussion: Hypereosinophilic syndrome with PDGFRA mutation has been associated with renal TMA in only a few reported cases. It has been hypothesized that eosinophil granule proteins lead to the endothelial injury and platelet activation that precipitates this form of renal injury. This case highlights the importance of early diagnosis of AKI in these patients and the need for prompt treatment.

Results: Between January 1, 2000 and December 31, 2019, 184,056 creatinine levels were enriched for 1,099 patients for the period from day -42 before to day +118 after ASCT. The overall incidence of AKI was 87% (n=956). 782 (71%) Patients have shown an AKIN 1, 145 (13%) an AKIN 2 and 29 (3%) an AKIN 3. During the observation period 122 (11%) patients died. For 32% (204/644) the transition to CKD has been observed.

Conclusions: AKI after ASCT is the rule and not the exception. As the vast majority of patients show AKIN 1 it might be often clinically overlooked. However early intervention might mitigate the development of long term renal impairment. Automated detection (AKI alert systems) as well identification and avoidance of factors contributing or aggravating injury (e.g., conditioning, immunosuppression, perfusion, inappropriate dosing of drugs) might minimize long-term renal complications in ASCT.

PUB245
Deep Analysis of AKI and CKD in Allogeneic Stem Cell Transplantation: A Big Data Approach
Nicole Brauer,1 Jan T. Kielstein,2 Catherina Lueck,1 Elke Dammann,1 Luca-Marie Heinze,1 Victoria Paragiota,1 Sophia Koehler,1 Hans Laser,1 Svetlana Gerbel,1 Michael Stadler,1 Matthias Eder,1 Gernot Beutel.1 HON Circle of the iCHOP initiative (www.ichop.eu) 1Hannover Medical School Enterprise Clinical Research Data Warehouse, Hannover, Germany; 2Academic Teaching Hospital Brunswick, Clinic for Nephrology, Rheumatology and Blood Purification, Brunswick, Germany.

Background: Acute kidney injury (AKI) is a common complication in allogeneic stem cell transplantation (ASCT). Although it is thought that in the majority of patients this injury is short lived in some patients, the damage persists for more than 3 months progressing into chronic kidney disease (CKD). So far, just a few publications have shown robust data based on larger patient populations. The aim of this project is to analyze the incidence and severity of AKI in ASCT and the transition into CKD.

Methods: Between 2000 and 2019, 1,401 patients underwent ASCT in our clinic. For 1,099, a detailed history of creatinine (n=184,056) could be extracted from the Clinical Data Warehouse. The classification of AKI was carried out in accordance with creatinine criteria of KDIGO classification at the respective stages (AKI 1, 2, 3). For AKI, an increase in serum creatinine of ≥0.3 mg/dL (26.5 micromol/l) within 48 hours or an increase in serum creatinine to ≥1.5 times baseline was used. Persistence of impaired renal function beyond day 90 was defined as CKD. An algorithm was programmed for the analysis of the big data and classification of the AKI / CKD. Retrospectively, the results were validated by a colour-coded representation of renal function.

Results: Between January 1, 2000 and December 31, 2019, 184,056 creatinine levels were enriched for 1,099 patients for the period from day -42 before to day +118 after ASCT. The overall incidence of AKI was 87% (n=956). 782 (71%) Patients have shown an AKIN 1, 145 (13%) an AKIN 2 and 29 (3%) an AKIN 3. During the observation period 122 (11%) patients died. For 32% (204/644) the transition to CKD has been observed.

Conclusions: AKI after ASCT is the rule and not the exception. As the vast majority of patients show AKIN 1 it might be often clinically overlooked. However early intervention might mitigate the development of long term renal impairment. Automated detection (AKI alert systems) as well identification and avoidance of factors contributing or aggravating injury (e.g., conditioning, immunosuppression, perfusion, inappropriate dosing of drugs) might minimize long-term renal complications in ASCT.

PUB246
Gemcitabine-Induced TMA: A Rare Side Effect Associated with High Mortality: A Case Report of Partial Response to Eculizumab
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Introduction: Thrombotic Microangiopathy (TMA) is a well-known complication in cancer, and it could be secondary to neoplasms itself or to its treatment. Gemcitabine-induced TMA is rare, but associated with high mortality rate and negative renal prognosis.

Case Description: A 71-year-old woman treated with Gemcitabine for recurrence of endometroid carcinoma developed a rapid progressive kidney injury, hypertension and pulmonary edema. Laboratory tests revealed signs of TMA. Histological analysis showed both acute and chronic TMA signs (Fig. 1). Upon suspicion of GitMA, antiblastic therapy was discontinued and, in order to prevent complement activation, Eculizumab was administered. According to literature, a sudden improvement of blood count was observed. Because of worsening of renal function, dialytical treatment was started. Histologically chronic lesions were documented (Fig.2).

Discussion: GitMA is mostly misdiagnosed, because blood count instability and renal impairment could recognised multiple triggers in neoplastic patients. An early diagnosis enables drug withdrawal and complement system inhibition: the only measures that seem to be associated with increased survival and a better renal outcome.

Focal mesangiolysis, glomerular basement membrane reduplication (Silver Jones stain; 400x)
Mesangiolysis, endocapillary proliferation (arrow), glomerular basement membrane reduplication; arteriole (asterisks) free from TMA signs (PAS stain; 400x)
Electrolyte Disorders Associated with the Use of Immune Checkpoint Inhibitors: A Single-Center Cohort

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Background: Electrolyte imbalances have been reported in association with exposure to immune check point inhibitors (ICI). However, the incidence of these disorders has not been widely established. Herein, we report a single center experience on the incidence of electrolyte abnormalities associated with ICI therapy as well as risk factors associated with their development.

Methods: We conducted a retrospective review of medical records searching for patients who received ICI over a 10-yr period at Ochsner Health. Demographic and clinical characteristics were extracted up to 1 yr post ICI treatment. Common Terminology for Cancer Adverse Events version 5.0 criteria were used to grade the severity of electrolyte abnormalities. Risk factors were examined by logistic regression.

Results: A total of 102 patients were identified. The mean age was 64 ± 11 years, 43% women, 82% of white race. Pembroliuzumab was the most commonly used ICI (46%), followed by nivolumab (26%) and atezolizumab (15%). The mean baseline glomerular filtration rate is 58 ml/min. ICI was more frequently administered to patients with lung cancer (47%). The incidence of hyponatremia (<134 mEq/L) and severe hyponatremia (<124 mEq/L) were 17% and 2%, respectively. Hypocalcemia (<8.4 mg/dL) was observed in 7%, whereas 11% experienced hypomagnesemia (<1.5 mg/dL) and 3% hypokalemia (<124 mEq/L) were 17% and 2%, respectively. Hypocalcemia (<8.4 mg/dL) was observed in 7%, whereas 11% experienced hypomagnesemia (<1.5 mg/dL) and 3% hypokalemia (<3.4 mEq/L). Melanoma was found to be numerically associated with hyponatremia, but not statistically significant (OR 3.1, 95% CI 0.7-14.8). White race was associated with 3 times greater risk of hyponatremia with ICI therapy (OR 3.5, 95% CI 1.2- 9.9). Although co-administration of cisplatin, underling chronic kidney disease and use of SSRI are known risk factors associated with hyponatremia, those variables were not associated with hyponatremia in our cohort, suggesting that hyponatremia secondary to use of ICI could be mediated by a mechanism independent of those variables.

Conclusions: Exposure to ICI is associated with the development of electrolyte imbalances. In our study, white race was identified as factor having 3 times higher odds of hyponatremia. Further studies are needed to examine race and other factors and the risk of hyponatremia in patients treated with ICI.

Spontaneous Tumor Lysis with Normal Electrolytes


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Introduction: Tumor lysis syndrome (TLS) leading to renal failure can occasionally occur prior to treatment in highly proliferative hematological malignancies. We present a case of AKI due to spontaneous TLS without the typical antecedent electrolyte derangements normally expected with TLS.

Case Description: A 76-year-old male with no prior medical history presented to the emergency room with abdominal pain and weight loss. CT scan revealed a gastric mass, ascites and abnormal liver consistent with cirrhosis. Gastric biopsy revealed diffuse large B cell lymphoma. He initially had a bland UA and a slight increase in baseline creatinine. The primary team treated him for hepatorenal syndrome with no response. No other pathology would explain the degree of renal failure further limiting the excretion of potassium and phosphate, making the diagnosis of pseudohyopotassemia. Following a biopsy, the patient remained anuric. A follow up UA showed protein and blood. Although the uric acid (UA) was 13.7 mg/dL, the phosphorous and potassium remained in their normal ranges leading us away from a diagnosis of TLS and toward the possibility of a rapid progressive glomerulonephritis. On biopsy the renal tubules contained calcium oxalate and calcium phosphate crystals with vacuolization of the tubular epithelial cells and tubular changes consistent with prior uric acid crystal deposition. The glomeruli were normal. At this point the uric acid level had risen to 25 mg/dL. Raisunibase was initiated and the patient eventually recovered renal function.

Discussion: In TLS, tumor cells lyse and release their intercellular electrolytes and purines (which are metabolized to uric acid) leading to elevated potassium, phosphorus and uric acid. Rarely the potassium and phosphorus can be normal. Our patient had renal failure further limiting the excretion of potassium and phosphate, making the normal levels of these electrolytes especially identifiable. Notifying the mechanism of normokalemia and normophosphatemia in spontaneous TLS may give us insight on how to diagnose it earlier, thus leading to earlier treatment.
PUB250

Pattern of Renal Diseases Detected on Renal Biopsy at Pakistan Institute of Medical Sciences (PIMS) Islamabad

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Background: Renal biopsy is an important tool for evaluation and diagnosis of glomerular, vascular, tubulointerstitial and genetic kidney diseases. It helps in determining the stage of disease, making treatment protocol and predicting prognosis as well. Purpose of the study is to find out pattern of renal diseases diagnosed on renal biopsies.

Methods: This is retrospective analysis done from February 2012 to April 2018. This data was taken from pathology department of Pakistan Institute of Medical sciences Islamabad Pakistan. These were adult patients above 18 years who underwent percutaneous renal biopsy due to some clinical indications. Their data was analyzed for spectrum of kidney disease on renal biopsy.

Results: Total biopsies were 254. Most common lesions were glomerular lesions. Among them primary forms were found. Most common GN found was Membranous Nephropathy (14%), second most common lesion was Focal segmental glomerulosclerosis (FGS) (12.5%) followed IgA Nephropathy (10.6%) Membranoproliferative glomerulonephritis MPGN (9.1%). Most common secondary glomerular lesion was found was Lupus Nephritis (7.8%). Other lesions were chronic kidney disease (12.5%), Interstitial fibrosis with tubular atrophy (IFTA) (5.9%), Rapidly progressive GN (5.9%), Renal cortical necrosis (4.3%), Acute tubular necrosis (ATN) (4.3%), IgM Nephropathy 2%, chronic tubulointerstitial disease (TID) (2.4%), Diabetic Kidney disease (DKD) (2%) Minimal Change Disease (2%), Amyloidosis AA (1.2%), HTN (0.8%), pos-streptococcal GN (0.8%), Postinfectious GN (0.4%), diffuse proliferative GN (0.4%). In young patients’ glomerular lesions were common whereas in middle age and elderly Chronic tubulointerstitial diseases and DKD were the common lesions.

Conclusions: In review of renal biopsies most common histological lesion found was membranous nephropathy (12.5%) followed by focal segmental glomerulosclerosis (FGS) (12.5%) and IgA Nephropathy (10.6%).

PUB251

Can Antinuclear Antibody (ANA) Be Monoclonal? A Case Report of Unusual Immunofluorescence Findings in a Patient with Monoclonal Gammopathy of Uncertain Significance (MGUS)

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Introduction: Nuclear staining by immunofluorescence in a kidney biopsy is often seen in patients with positive ANA in the serum. These ANA are usually polyclonal, but herein we report an unusual finding by immunofluorescence of IgG2 lambda monoclonal nuclear staining in a patient with MGUS.

Case Description: The patient is a 72-year-old Caucasian male with a history of diabetes mellitus type 2 (hemoglobin A1c is 6.1%) who was recently treated with hydroxyzine, and he was found to have positive ANA (homogenous pattern, > 320), but after discontinuation of hydroxyzine the ANA decreased to 21. He had positive P-ANCA (positive MPO), 4 and negative C-ANCA (negative PR3). Also he has positive anti-double-stranded DNA. His serum creatinine was 1.7 mg/dl (1 mg/dl baseline), proteinuria 0.34 gm/24h. He did not have monoclonal protein in the urine, but in the serum by immunofluorescence there was IgG lambda monoclonal protein (two monoclonal bands were noted). He has elevated serum both kappa and lambda light chains with normal kappa-to-lambda light chain ratio. Kidney biopsy showed acute tubular necrosis (ATN), moderate chronic kidney injury and there was no evidence of immune complex deposition, monoclonal immunoglobulin deposition or amyloid. Immunofluorescence showed positive nuclear staining for IgG (IgG2 subclass only) and lambda but not kappa light chain (Fig 1). These findings raise the possibility that his ANA are of monoclonal origin.

Discussion: Our case demonstrates the unique pattern of IgG2 lambda monoclonal nuclear staining by immunofluorescence in the patient with MGUS. The prevalence of this type of findings is not well studied.

PUB252

The Use of Bone Wax to Position and Secure the Kidney for Intravital Analysis in Mice Using an Abdominal Imaging Window

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Background: Intravital imaging is a powerful technique for evaluating inflammatory processes, cell migration, tubule and blood flow, cyst development, and injury and repair responses in vivo in live kidneys. Combining this with the use of an abdominal imaging window (AIW) allows for long-term in vivo visualization. However, the challenge has been preventing the kidney from repositioning in the AIW over the course of the study. Previous methodology utilized a cyanoacrylate adhesive to attach the kidney to the window or gauze placed under the kidney to stabilize it against the window, thus facilitating the acquisition of images. In our hands, both approaches cause scarring and fibrosis that have complicated our analysis. Here we compare a bone wax approach to secure the kidney with that of gauze.

Methods: AIW implantation surgery was done on 8 to 10 week old wild type mice and the kidneys were positioned and secured in the window using sterile gauze or bone wax (n=4 each).

Results: Our results show that sterile gauze can cause adhesion reactions with the surrounding tissue, including the kidney, making it difficult to visualize and image the kidney for more than 3 days post window insertion. In addition there are inflammatory reactions, and the kidney frequently adhered to the AIW overslip preventing imaging of cell movements, cilia responses, and flow within the renal tubule. Bone wax is an inert and malleable substance that is used for bone recovery surgeries and therefore should not result in an intense inflammatory response. In contrast to the results obtained with sterile gauze, using bone wax to secure placement of the kidney in the window resulted in a far less inflammatory reaction and reduced adhesions and fluid accumulation within the window. Using bone wax, we can now easily follow the kidney for 2 - 3 weeks after surgery with minimal complications.

Conclusions: We conclude that bone wax is a superior approach for long-term intravital renal imaging. The longer time frame provided by using bone wax for longitudinal renal visualization will allow us to evaluate the initiation and expansion of cysts, to image renal injury responses and cell movements, and to analyze tubule flow and cilia responses.

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PUB253
Renal Tuberculosis: An Uncommon Presentation of a Common Disease: Case Report
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Introduction: Renal tuberculosis is an endemic country for tuberculosis (TB) with 3 500 cases per year, 85% correspond to pulmonary presentation. Genitourinary tuberculosis is uncommon, it is considered a severe form of extrapulmonary TB; it is secondary to infection with Mycobacterium tuberculosis complex with a long-standing dysuria, sterile pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB having hematuria and fever as the only clinical features.

Case Description: A 54-year-old Guatemalan male came to the emergency room with a history of intermittent fever during the last year that worsens in the last 2-weeks. He lived in a rural area at the southern-coast of Guatemala. No previous medical history, no pets at home. The fever was between 38.3-40°F with a history of intermittent fever during the last year that worsens in the last 2-weeks. His physical exam showed pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB infection with Mycobacterium tuberculosis complex with a long-standing dysuria, sterile pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB in various conditions.

Discussion: Renal TB has a prevalence of 10% worldwide and 20% in Latin-America mainly from pulmonary origin. The reported cases have higher prevalence in developing countries, male gender, immunosuppressed state as in HIV infection and post-transplanted. It is an under-diagnosed disease that can lead to CKD. The diagnosis of renal TB must be considered in patients with dysuria, hematuria, pyuria with negative urinary cultures.

PUB254
Real-Time Percutaneous Kidney Biopsy Experience: Is There a Change in the Trend of Complication?
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Background: Percutaneous kidney biopsy (PRB) is essential in establishing diagnosis and guides in the treatment of renal diseases. The procedure of kidney biopsy has evolved through technique and procedural refinements. Bleeding and its consequences are the most concerning complications of kidney biopsy. This is a UK renal centre experience to report the post-kidney biopsy bleeding complications.

Methods: We included all patients (inpatient and day case) who underwent PRB between January 2014 and Dec 2016. Biopsy was performed using a 16-gauge biopsy needle with a spring-loaded trigger device. Pre-biopsy parameters such as Blood pressure, haemoglobin, platelet counts and coagulation studies of patients were recorded. Data on kidney biopsy outcome were collected retrospectively. Bleeding complications were microscopic hematuria, drop in haemoglobin requiring blood transfusion or requiring intervention radiology. Statistical analysis was performed.

Results: A total of 458 kidney biopsies were carried out with 58.9% male and 51.1% as day case. There was a 2.4% technical failure and 96.9% histological adequacy. Indications for kidney biopsy were acute kidney injury (37.1%), nephrotic syndrome (24.5%), proteinuria (17.7%) and hematuria (8.2%). Histopathology diagnoses were IgAN (12.2%), punc-immune glomerulonephritis (10.4%), tubulointerstitial nephritis (9.3%), FGSS (7.6%), diabetic nephropathy (7.1%) and membranous glomerulonephritis (6.4%). Bleeding episodes were seen in 19.4% (3.0%) haematomata and 10.2% (patient) had embolisation. Day case (2.1%) compared to in-patient (6.8%) kidney biopsy and platelet count (>100 x 10^9) had less bleeding complication (p<0.05). Median serum creatinine in the group the group inpatient kidney biopsy (136.9 ± 26.4 vs. 151.21 ± 94.2, p<0.005). In-patient kidney biopsy were older, had lower hemoglobin and higher INR (p<0.05). Lower mean hemoglobin (104.4 ± 15.39 vs. 115.3 ± 21.03, p=0.025) and higher mean serum creatinine (413 ± 288.41 ± 242.16 ± 185.72, p=0.005) were detected in those who had hematuria. We reported no nephrectomy or death.

Conclusions: We report a low post kidney biopsy bleeding complication. Day-case procedure has a lower rate of kidney biopsy bleeding complication when compared to in-patient kidney biopsy.

PUB255
Variation in Interpretation of 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) in Children with Confirmed or Suspected Hypertension (HTN) by Canadian Pediatric Nephrologists and Cardiologists Isabella Stefanova,1 Abdalaziz A. Bamhaz,2 Anne Fournier,3 Kevin Harris,4 Guido Filler,1 Damien G. Noone,1 Janis M. Dionne,1 Rahul Chanchlani,1 McMaster University, Hamilton, ON, Canada; 2Master Children’s Hospital, Hamilton, ON, Canada; 3Western University Schulich School of Medicine & Dentistry, London, ON, Canada; 4Sick Kids Foundation, Toronto, ON, Canada; 5BC Children’s Hospital, Vancouver, BC, Canada; 6Université de Montreal, Montreal, QC, Canada.

Background: ABPM is more accurate compared to a single office blood pressure (BP) measurement. However, it is unclear how physicians interpret ABPM and make management choices, especially where evidence supporting recommendations is limited. This survey’s goal is to identify ABPM interpretation variation by HTN category and disease among pediatric nephrologists and cardiologists.

Methods: Survey content included physician demographics, ABPM indications, interpretation, and management. The same questions were asked of all respondents, except kidney-related conditions which were only shown to nephrologists.

Results: The survey was sent to 196 physicians, with 69 (35.2%) responses. Most respondents were age 45+, in practice for 11+ years and university-based. Table shows significant differences in ABPM interpretation for BP load, isolated systolic and diastolic HTN, and between nephrologists and cardiologists for different conditions (not all data included in abstract table). Rates of HTN treatment are lower than guidelines recommendations.

Conclusions: There is significant practice variation among physicians in ABPM interpretation and management. Gaps in guidelines create ambiguity regarding management decisions for different ABPM parameters. A more protocolized approach may help to standardize practice.

Initiation or alteration of antihypertensive treatment with respective ABPM parameters in various conditions.

PUB256
An Electronic Health Record (EHR) Algorithm to Identify Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD) Eric Benz,1 Amy Goodwin Davies,1 Hanieh Razzaghi,1 Lisa M. Guay-Woodford,2 Charles Bailey,3,4 Erum A. Hartung,1,5 The Children’s Hospital of Philadelphia, Philadelphia, PA; 1University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 2Children’s National Hospital, Washington, DC.

Background: ARPKD is an important cause of pediatric chronic kidney disease, hepatic fibrosis, and portal hypertension. Its rarity makes it difficult to collect larger-scale natural-history data and to identify patients for clinical trials.

EHR-based algorithms identify ARPKD patients at a single site in PEDSNet (v3.9, 1/2009-7/2020), a national pediatric learning health system. A training/testing cohort consisted of 50 clinician-confirmed ARPKD patients and 150 non-ARPKD controls (enriched for patients with cystic/dysplastic diagnoses). A random forest was implemented to classify patients as cases and non-cases, with variable importance permutation-based, with high performance (precision 98%, recall 94%). The natural history data and to identify patients for clinical trials.

Results: The key model selection features were number of visits with an ARPKD diagnosis code and presence of a hepatic fibrosis diagnosis code. Table 1 shows patient characteristics. Of 97 patients reviewed, clinicians excluded 5 as indeterminate, and classified 56 as non-ARPKD and 36 as ARPKD [positive predictive value (PPV) of an ARPKD diagnosis 39%]. The algorithm identified 23 true positives, 17 false positives, 1 negative and 1 indeterminate diagnosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

836
13 false negatives, and 39 true negatives; model performance: sensitivity 64%; specificity 70%; PPV 58%; negative predictive value (NPV) 75%.

Conclusions: An EHR-based algorithm improves PPV for identifying patients with ARPKD compared to diagnosis code alone and has relatively good NPV for excluding ARPKD in non-ARPKD patients with an ARPKD diagnosis code in their chart. Further chart review of incorrectly classified patients will allow algorithm refinement to improve performance.

Funding: NIDDK Support

PUB257
Nitromethane Fuel Toxicity Causing False Elevation of Serum Creatinine
Vimal, Nitomethane along with methanol is a common component of model airplane, rocket fuel and race car fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffe reaction analysis has been reported in adult literature with limited pediatric data being available.

Introduction: Nitromethane along with methanol is a common component of model airplane fuel, rocket fuel and race car fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffe reaction analysis has been reported in adult literature with limited pediatric data being available.

Case Description: 12 year old male with past medical history significant for major depressive disorder in remission on prozac, H/O medium chain acyl-CoA dehydrogenase (MCAD) deficiency on a low fat diet and levocarnitine. Patient had prior admissions for self-harm and presented after ingesting about a mouthful of Torco race fuel. On initial evaluation in outlying ER, he was hemodynamically stable with heart rate of 97 per minute, respiratory rate of 16 breaths/min with saturations of 97% on room air and BP recorded at 130/67. Initial lab check showed a normal creatinine at 0.69 mg/dl. Patient was transferred to our hospital for administration of fomepizole as methanol is a main component of Torco race fuel. On arrival, repeat labs in 5 hours showed an increase in creatinine to 1.73, which slowly started coming down to 1.39, 48 hours into admission. He remained normotensive for administration of fomepizole as methanol is a main component of Torco race fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffe reaction analysis has been reported in adult literature with limited pediatric data being available.

Discussion: This is a pediatric case report on Torco race fuel ingestion in which the ingredient nitromethane (CH₃NO₂) caused a false elevation of serum creatinine. The standard assay for creatinine uses the Jaffe reaction, an alkaline picrate colorimetric assay for creatinine and alkaline picrate. Nitromethane by its reactive methyl component interacts with alkaline picrate producing a cromophore that closely resembles the creatinine picrate cromophore. Enzymatic assay of creatinine, which with alkaline picrate producing a cromophore that closely resembles the creatinine picrate cromophore. Enzymatic assay of creatinine, which

PUB258
Long-Term Renal Outcomes of Congenital Ureteropelvic Junction Obstruction
Alexandra Stewart, John S. Thurlow, Stephen W. Olson, Brent L. Lechiner, Sarah Khan, Erin D. Parker, Maura A. Watson, Christina M. Yuan, Robert Nee, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Congenital ureteropelvic junction obstruction (UPJO) is often diagnosed in adulthood. Current literature is lacking in evaluation of long-term renal outcomes for adult patients with UPJO.

Methods: We queried service members diagnosed with UPJO from the U.S. Military Health System electronic health records. We assessed demographic, laboratory, radiology, stenting/pyeloplasty and outcome data. We assessed the impact of intervention regarding development of chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², hypertension (HTN) (blood pressure ≥130/80 mmHg), and changes in renal excretory function on radionuclide scans.

Results: We identified 108 individuals diagnosed with congenital UPJO; mean follow-up of 7 years. 55% had right-sided, 40% left-sided and 5% bilateral UPJO. Mean age at diagnosis was 25 years (n=10 <18 years; n=98 at ≥18 years); 95% male; 69% White, 15% Black. At diagnosis, mean BP was 130/78 mmHg; mean eGFR 86 ml/min/1.73m²; and 22% had proteinuria ≥30mg/dL 85.2% had pyeloplasty and 23.4% had low renin placement. 14% developed eGFR <60 ml/min/1.73m². 9.5% of patients with intervention developed stage 3 CKD vs. 21.4% of those without intervention (p=0.42). Intervention was not associated with development of HTN in adjusted logistic regression analysis (OR 0.30, 95% CI 0.08-1.20). Intervention significantly reduced the proportion of patients with delayed cortical excretion and T/β emptying time with right-sided UPJO only (Table).

Conclusions: Approximately 14% of our young adult cohort with congenital UPJO developed CKD. Intervention improved cortical excretion and T/β emptying time with right-sided UPJO only. The views expressed are those of the authors and do not reflect official policy of the Dept of the Army/Navy/Air Force, Dept of Defense, or US government.
Building the Bridge Between Pediatric and Adult Nephrology: A Quality Improvement (QI) Approach for Health Care Transition (HCT)  

Sahar Siddiqui,1,2 Cortney T. Zimmerman,1,2 Constance M. Wiemann,1,2 Sai Kaumudi Sardrey,1,2 Baylor College of Medicine, Houston, TX; Texas Children’s Hospital, Houston, TX.

Background: HCT from pediatric to adult-focused care in patients with renal disease continues to be difficult, we know that an inadequate HCT process can lead to poor patient outcomes. Various studies have demonstrated utilization of a HCT clinic as a means to improve communication and satisfaction between adolescents/young adults (AYA) and providers. This abstract highlights a QI approach conducted in the pediatric nephrology department of a children’s hospital in collaboration with adult nephrology providers at an affiliate hospital in the Southwestern USA.

Methods: A dedicated transition team was created at the pediatric nephrology section which participated in transition needs assessment (Fig. 1). Part of this assessment involved surveys to pediatric faculty (n = 14), who rated the current transition process. A pilot group of patients was proposed to lead this effort with initiation of a novel form of transition clinic; 2-step transition clinic to tackle lack of a dedicated transition clinic. This clinic provides patient interaction with their renal providers and multi-disciplinary support in at least two different health care settings, pediatrics followed by adult.

Results: Multiple barriers were identified by initial needs assessment including lack of standardized transition procedure. Ease of transition was rated as 2.5 out of 5 (a 5 being easiest transition). During this endeavor, our team was able to build a framework for HCT along with strengthening ties with our adult colleagues. We collected surveys from patients at the time of 2-step transition clinic (n = 10) which was overall reassuring however 50% of the patients felt “somewhat ready for transition” highlighting the need for better transition preparedness.

Conclusions: The needs assessment underscores areas to target for intervention. We propose that implementation of the new standardized process including our 2-step transition clinic will result in enhanced patient satisfaction and HCT outcomes with potential areas for improvement.

Impact of Hypertension on Health-Related Quality of Life in Childhood-Onset Systemic Lupus Erythematosus  

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Background: Childhood onset SLE can significantly impact Health-related quality of life (HRQOL) due to disease manifestations and its associated therapies. Hypertension is another chronic disease that can impact the HRQOL in children despite its “silent nature.” In cSLE, secondary HTN can occur in up to 70%, due to nephritis and/or interstitial fibrosis and tubular atrophy (IFTA), 52.4% had 1~<25% IFTA, 17.1% had IFTA ≥25%~50% and 4.9% had IFTA ≥50%. Most pts (79.3%) exhibited 25% glomerular sclerosis while 9.2% had ≤50% GS.

Conclusions: FSGS in this pediatric population was associated with low degrees of glomerular sclerosis, interstitial fibrosis and tubular atrophy, but severe foot process effacement was common. When comparing to data reported in a companion abstract in adult pts with FSGS, the lower levels of sclerosis and fibrosis observed in these pediatric FSGS pts, suggest that early and effective intervention could potentially aid long term renal survival.

Funding: Commercial Support - Traveve Therapeutics
PUB263
Parenteral Iron and Erythropoietin Effects on FGF-23 and Cardiac Function in Young Dialysis Patients
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Background: Elevated fibroblast growth factor 23 (FGF23) levels are associated with left ventricular hypertrophy (LVH) and diastolic dysfunction (DD). Recent preclinical and adult human studies have shown that parenteral iron (Fe) supplementation and erythropoietin (EPO) may increase FGF23 production and circulating levels. Whether treatment with EPO or Fe could increase FGF23 levels and adversely contribute to LVH and DD in pediatric patients maintaining hemodialysis (HD) remains largely unknown.

Methods: Adolescents (n=20, median age 16 years) maintained on HD (average dialysis vintage 30 ± 17 months) were studied. All were treated with EPO, with or without concomitant parenteral Fe sucrose and all received intravenous paricalcitol for secondary hyperparathyroidism. C-terminal FGF23 (eFGF23), biochemical markers, and sequential echocardiograms (conventional and tissue Doppler, ECHO) were analyzed longitudinally twice, 6 months apart. LV dimensions, including IVST (interventricular septal thickness) and markers of diastolic function with peak early (E), late (A) diastolic flow velocities, and corresponding mitral annular velocities (Em, Am) were measured, and adjusted to Z-scores according to age and gender.

Results: Whereas the cumulative average EPO dose was similar in Fe-treated and untreated patients (10,056 ± 5,445 and 10,818 ± 7,935 Units/week/6 months, respectively), the initial and final eFGF23 levels remained similarly elevated in both groups. Prevalence of DD improved from 22% to 12% during the study period. Log[FGF23] values correlated with Am (r = -0.7) and Em/Am (r = 0.7) Z-scores (both p<0.05) in Fe-treated patients. The doses of EPO and Fe did not correlate with markers of diastolic function, but EPO correlated with the IVST Z-score (r = 0.7, p<0.05). The cumulative paricalcitol dose did not correlate with markers of diastolic function but inversely correlated with IVST Z-score (r = -0.5, p=0.05).

Conclusions: Treatment with EPO, irrespective of parenteral Fe supplement, hemoglobin, and ferritin levels did not result in consistent elevations of eFGF23 levels. While eFGF23 levels correlated with worsen markers of diastolic function, the overall prevalence of DD improved overtime. The administration of paricalcitol may have contributed to the improvement of DD and the LVH.

Funding: Clinical Revenue Support

PUB264
Is It Time to Update the Age-Specific Pediatric Normative Serum Creatinine Ranges?

Background: Diagnosis of abnormal kidney function is routinely based on serum creatinine (Scr) value. Scr in children increases with growth and normative values therefore vary with age. However, due to lack of availability of large number of blood samples from healthy children, most laboratories combine the SCR reference ranges in up to 5-year age group blocks, resulting in an upper limit that can be 2.3 to 2.6 times higher than the lower limit for that age block. As a result, a child with subnormal kidney function (GFR < 90 mL/min/1.73m2) who is near or at the younger end of the age in a specific age group block, can still have SCR value below the upper limit of reference range and thus will remain unflagged on the reported result. This may result in a missed diagnosis of decreased kidney function. Similarly, a diagnosis of acute kidney injury (SCR increase >1.5 above baseline) can also be missed as the increased SCR value can still fall within the reference range for that age group. In research studies, missing baseline creatinine values are customarily back calculated from eGFR equations with a presumed GFR of 120 mL/min/1.73m2. Our objective was to calculate age specific SCr reference ranges for children 2 – 18 years, and compare them with current age block group reference ranges.

Methods: We used bedside Schwartz equation (eGFR = height*0.413/SCr, where 0.413 is the constant k) to calculate estimated creatinine (eCr) = height*0.413/GFR. We calculated the eCr reference ranges by inserting 3rd percentile for height and GFR of 120 mL/min/1.73m2 for the lower limit, and by inserting 97th percentile for height and GFR of 90 mL/min/1.73m2 for the upper limit. Height values for respective ages were obtained from the CDC reference charts.

Results: The calculated theoretical reference ranges are shown in the Table. The upper limit of eCr values are only 1.6 times higher than the lower limit in contrast to the current reference ranges where the upper limit is 2.3 to 2.6 times higher than the lower limit for its age group block.

Conclusions: We believe that by switching from age group blocks to age specific normative SCR ranges the possibility of missing subnormal kidney function will be minimized. The calculated values need to be further validated.

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PUB265
Are Mutations in the Alpha-Hydroxy Acid Oxidase (HAO1) Gene Not as Harmless as Described?
Bernd Hoppe,1 Luisa Averdunk,2 Kathrin Buder,2 Cristina Martin Higuera,1
1German Hyperoxaluria Center, Bonn, Germany; 2University Childrens Hospital Zurich, Zurich, Switzerland; 3University Childrens Hospital Düsseldorf, Düsseldorf, Germany.

Introduction: Alpha-hydroxy acid oxidase (HAO1) catalyzes the oxidation of glycolate into glyoxylate in hepatic peroxisomes. Patients with homozygous HAO1 mutations have massively elevated urinary glycolate excretion (Uglyc), but are said to be clinically asymptomatic.

Case Description: We present three pediatric patients, who either developed clinical sequelae, here arrolithiasis (UL), or surprisingly had hyperoxaluria. First patient now 10 years of age, developed UL at age 6 years, which was treated by lithotripsy (stone analysis: 100% whewellite). Currently, he has 2 small stones in left kidney. Recent 24 h urine excluded elevated urinary oxalate excretion (UOx, 0.35-0.43), but high glycolate UGlyc (3.34-4.78 mmol/1.73m2/d). His grandfather also had recurrent UL, but normal UOx and UGlyc. Patient 2 was 6 months of age at diagnosis of elevated Uox and UGlyc (1.37 and 7.01 mmol/1.73m2/d, respectively). He has 3 relatives with a history of UL, elevated Uox/creatinine ratio was found in 2/3, and in the boys mother. Genetic evaluation for primary hyperoxaluria (PH) was negative. In patient 3 screening for organic acids detected elevated Uox: 1.56 and UGlyc: 7.04 mmol/1.73m2/d. Genetic testing for PH was negative. Vitamin B6 though let to decline in Uox. UGlyc remained significantly elevated. Homozygous (family) mutations in HAO1 were found also in parents, sister and in newborn brother. Father and sister also had elevated Uox (1.09 and 0.92) and UGlyc (4.19 and 4.75 mmol/1.73m2/d). The newborn has a massively elevated UGlyc/creatinine ratio, but no hyperoxaluria.

Discussion: In the contrary to current understanding, patients with HAO1 mutations can express a renal phenotype. We do not have an adequate explanation for UL in patient 1, as only UGlyc is elevated and no other risk factor is found. GO inhibition is used as therapeutic target in patients with PH1, which reduces Uox, but elevates UGlyc. Even more problematic to explain is the significant hyperoxaluria in patients 2 and 3 (after excluding secondary reasons). Therefore, the link between HAO1 (loss of function) mutations and UL, or hyperoxaluria, respectively, clearly needs further clarification.

PUB266
Characterization of Adolescents with Persistent Albuminuria in a Region with a High Prevalence of ESRD of Unknown Etiology

Background: We report high prevalence of ESRD of unknown etiology. Affected group was between 20 and 30 yo. We screen adolescents for chronic kidney disease (CKD).

Methods: Pts with Albuminuria-creatininuria ratio (ACR) ≥30 mg/gr or GFR ≤75 mL/min were reevaluated. Ultrasound (US) and tomography were performed. Renal bx was performed in pts with persistent albuminuria (PA).

Results: We include 482 pts, mean age 13.3±1.5, 33.9% were male. We detect 17 pts (3.53%) with PA. US did not show abnormalities. 16 bx were performed(Table1).

Conclusions: The characteristics of the biopsies are suggestive of established histological damage. Potential genetic and contaminants should be searched.
More Than “Getting High,” Be Aware of Cannabis-Induced AKI: A Report of Two Pediatric Cases

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Background: Cannabinoids (synthetic or natural) can have deleterious effects on kidneys. We report 2 cases of cannabis-induced acute kidney injury (AKI) with acute tubular necrosis (ATN) and acute interstitial nephritis (AIN). Methods: Case Series.

Results: Two adolescents were cared for in 2021, presented with elevated serum creatinine (S. Cr). At presentation S. Cr was 1.7–5.4 mg/dL, peaked at 5.4–6.6 mg/dL. Both patients developed acidosis. Patient 2 had hypokalemia, hypophosphatemia, and hypomagnesemia. Urine drug screen was positive for cannabinoids. Both patients were admitted to using natural cannabis predominantly and smoking cannabis joints daily for several years. They assumed that natural cannabis is safe. A thorough history including drug use should be obtained in cases of AKI, particularly where the cause is not apparent and AKI does not improve with hydration. Awareness of this could lead to early diagnosis, management, and appropriate counseling, which might potentially decrease kidney damage and scarring.

Conclusions: Though the endocannabinoid system (ECS) has been found to play a beneficial role in renal homeostasis and improvement of tubular cell survival, long-term stimulation and alterations to the ECS can lead to kidney damage as reported here. It is interesting to note that 2 patients predominantly used natural cannabis and reported that they assumed that natural cannabis is safe. A thorough history including drug use should be obtained in cases of AKI, particularly where the cause is not apparent and AKI does not improve with hydration. Awareness of this could lead to early diagnosis, management, and appropriate counseling, which might potentially decrease kidney damage and scarring.

Involvement of Succinate Dehydrogenase (SDH) in Deceased Kidney Donors’ Inflammation

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Background: Succinate is a Krebs cycle intermediate that is converted to fumarate by succinate dehydrogenase (SDH). SDH activity depends indirectly on the oxygen availability. In deceased renal donation, hypoxia associated to ischemic process can increase renal succinate formation and induce the infiltration of immune cells producing TNF-α, increasing inflammation, renal epithelial apoptosis, as well as leukocyte recruitment, binding and migration, which can lead to renal graft damage. Moreover, increased levels of IL-1β promoting inflammation. We aim to demonstrate that succinate pathway is an important player in early and late inflammation in deceased kidney transplants.

Methods: Relative gene expression of SDH complex genes (SDHA, SDHB, SDHC and SDHD), HIF-1α and inflammatory factors were quantified by qPCR in RNA samples from deceased donors. Succinate levels were measured in serum from deceased kidney donors at the time of donation.

Results: Circulating succinate levels in serum from deceased donors were significantly higher than in healthy volunteers (p=0.002). In kidneys samples from deceased donors, gene expression of all four subunits of SDH complex were downregulated before transplantation (p<0.001 for all of them) whereas HIF-1α was increased compared to living donors (p=0.001). SDHA, SDHB and SDHD gene expression at 4 months after kidney transplant was positively correlated with graft renal function (CKD-EPI). In kidneys from deceased and living donors, SDHA, SDHB and SDHD are negatively associated with recruitment (MCP-1), adhesion (ICAM-1) and activation (IL-1β) of monocyte.

Conclusions: Our results indicate that low gene expression of SDH in kidneys from deceased donors could result in reduced activity of SDH that would reduce the ability to transform succinate to fumarate resulting in succinate accumulation, increasing inflammation that can influence on kidney transplantation outcomes.
therapy. In this way, 28.6% of the recipients was treated with monotherapy with a calcineurin inhibitors and 21.5% with monotherapy with a mTOR inhibitor. In other hand, 16.7% received a combination of tacrolimus with a mTOR inhibitor. Rejections were not observed in our group and all the patients presented a preserved kidney function at the end of follow up. Four recipients died because of PTLD. The remaining 27 presented a complete response or stabilization of the disease.

Conclusions: Most of the PTLD were detected between 2016-2020. The time from transplantation to PTLD appearance was long, being EBV viral load negative in the majority of the cases. Graft survival after chemotherapy and reduction of immunosuppressive therapy was excellent, with a low risk of rejection and a good prognosis for hematology disease. It is possible that a reduction in immunosuppression in selected patients could prevent the development of PTLD.

PUB270
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Background: Preformed donor specific anti-HLA antibodies (pre-KT DSA) is one of the leading causes of post kidney transplant antibody mediated rejection (ABMR). Decrease level of pre-KT DSA by pre-transplant desensitization is one of the best available methods to lower risk of ABMR after transplantation. Post-transplant follows up of DSA to determine the persistence or clearance of DSA should reflect transplant outcomes. This study aimed to compared outcomes between patients who have persistence and patients who have clearance of DSA after kidney transplantation.

Methods: This retrospective cohort enrolled pre-KT DSA positive (CDC-AHIG negative) kidney transplant recipients (KTR) at King Chulalongkorn Memorial Hospital from 2009 to 2018. Post-transplant DSA was tested by Luminex single-antigen assays and divided patient in to two groups 1) DSA clearance (<1000 MFI) and 2) DSA persistence (>1000 MFI). The outcomes were evaluated that comprise biopsy-proven acute rejections, including acute antibody-mediated rejection (ABMR) and acute T cell-mediated rejection (TCMR), clinical or borderline rejections, and graft loss, allograft and mortality. Complications following KT and other associated risks were also assessed.

Results: There were 47 KTR enrolled. The mean pre-KT DSA (MFI) level was 931.37. Sixty percent of patients underwent pretransplant desensitization. The median follow-up time was 5.7 years after transplant. The persistence DSA group (n=17) had higher rate of ABMR than DSA clearance group (n=30), with hazard ratio (HR) of 4.47 (95% CI, 1.48 – 13.45, p=0.008). Factors associated with persistence DSA include the recipient’s age of over 40 years old, higher number of HLA class I/II mismatch, and lower tacrolimus levels at six months.

Conclusions: DSA should be monitored in kidney transplant patient with pre-KT DSA. The persistence of pre-KT DSA after kidney transplantation is associated with higher rate of ABMR. Surveillance allograft biopsy should be performed in patient with persistence DSA for early detection of rejection.

PUB271
Angiosarcoma in a Kidney Transplant Recipient with Fibrillary Glomerulonephritis
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Introduction: Kidney transplant recipients are at increased of developing malignancy. Angiosarcoma (AS) are aggressive tumors arising in either blood or lymphatic vessels. Fibrillary glomerulonephritis (FGN) has been described in the setting of malignancies. Here we present a case of metastatic angiosarcoma that developed in a patient with a history of end-stage kidney disease (ESKD) secondary to FGN.

Case Description: A 66-year-old female with ESKD secondary to FGN underwent five-antigens mismatch living unrelated donor kidney transplant with thymoglobulin and methylprednisolone induction. Pre-transplant workup showed no malignancy. Immunosuppression included tacrolimus, mycophenolic acid, and prednisone. Three months post-transplant, she had a scalp lesion diagnosed as eczema, which improved partially with topical steroids. Four months post-transplant, the lesion increased in size and developed abdominal discomfort with distention. Imaging showed widespread lymphadenopathy, numerous liver lesions, splenomegaly, and ascites. An excisional lymph node biopsy from the neck revealed AS. She developed acute kidney injury with gross hematuria. Urine microscopy revealed numerous intact RBCs but no other abnormal findings. Due to volume overload with low serum albumin (2 g/dl), she was given intravenous albumin and furosemide, and her creatinine improved. Tacrolimus and mycophenolate were stopped, and sirolimus was started. Weekly paclitaxel was initiated, but she developed febrile neutropenia and deconditioning after the second dose, for which she opted out for further chemotherapy. Nine months post-transplant, follow-up showed dramatic clinical improvement with complete resolution of scalp lesions. Imaging showed markedly decreased conspicuity of low attenuation observations in the liver and a marked decrease in mesenteric and retroperitoneal lymphadenopathy. Kidney function remained at baseline.

Discussion: Angiosarcoma is a rare yet aggressive tumor with a poor prognosis in kidney transplant recipients. Here, the dramatic response may have resulted from lowering immunosuppressive drugs and starting chemotherapy. However, the anti-angiogenic activity of mTOR inhibitors is a possible explanation. Most reported AS cases developed from arteriovenous fistulas in kidney transplant patients. This is the first case of AS with FGN with an unexpected dramatic improvement.

PUB272
Recurrence of Scleroderma Renal Crisis After Kidney Transplantation
Juran P. Portocarrero Caceres, Cybele Ghosein, Yashpal S. Kanwar. Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: Diffuse cutaneous Systemic Sclerosis (dcSSc) is a disease of generalized inflammation, vascular damage, and organ fibrosis. Scleroderma Renal Crisis (SRC), one of the most devastating complications of dcSSc occurs in 5-20% of patients and leads to end stage renal disease (ESRD) 20-50% of the time. SRC is characterized by malignant hypertension and acute kidney injury (AKI). Thrombotic microangiopathic anemia (TMA) and heart failure (HF) can also be seen. SRC patients with ESRD can undergo kidney transplantation (KT) with excellent graft survival. Recurrence of SRC in KT is very rare presumably because the renal vasculature is from a donor kidney without dSSc. We report a case of SRC in a patient post KT.

Case Description: A 52-year-old male-to-female transgender patient with a history of ESRD due to SRC, who had a living unrelated KT 2 months prior to admission is admitted with hypertension and pulmonary edema. She was found to have BP with reduced ejection fraction (37%) and a new pericardial effusion and AKI. Kidney biopsy showed arteriolar walls with thickened walls, bland arteriolitis with semi occlusive changes. She was diuresed and discharged home. She returned 2 weeks later with microangiopathic hemolytic anemia, thrombocytopenia, and worsening kidney function. Repeat kidney biopsy was consistent with TMA. Given her clinical presentation and biopsy findings, a presumptive diagnosis of SRC was made. The patient was also found to have an antibody-mediated rejection. She received cyclophosphamide, multiple sessions of PLEX, eculizumab, and belatacept, without response. She was initiated on dialysis where she remains today.

Discussion: SRC post KT is unusual but should be considered in the differential of AKI in the right clinical setting. Active dcSSc disease, use of steroids and calcineurin inhibitors may increase the risk of post transplant SRC.

PUB273
Kidneys with Kidney Donor Profile Index (KDPI) >85% Can Be Used Successfully in Older Recipients
Muna Alnimir. University of California Davis, Davis, CA.

Background: Kidneys with KDPI >85% have high discard rate approaching 50%, transplanted elderly patients over the age of 55 have lower risk of all cause mortality and death caused by cardiovascular disease compared to their counterparts on dialysis. We present one year clinical outcomes of High KDPI > 85% kidneys when transplanted in elderly recipients.

Methods: Retrospective analysis of kidneys with KDPI >85% transplanted in UC Davis Medical Center between 1/1/2016 and 12/30/2018.

Results: 67 patients received kidneys with KDPI >85% between 1/1/2016 and 12/30/2018, 77.5% were males, 52.2% diabetics, mean recipient age was 64.5 years, 41.8% developed delayed graft function staying on dialysis for a mean of 17 days, 82% were alive after one year, 3 kidneys failed 81.5 % of kidneys were functioning after one year with mean creatinine of 1.4mg/dl.

Conclusions: KDPI >85% kidneys can be used successfully in older kidney recipients avoiding dialysis exposure and expanding the donor pool.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PUB274
Risk Factors and Outcomes of BK Viremia Among Deceased Donor Kidney Transplant Recipients Based on Donor Characteristics
Isabel C. Breyer, Ban E. Dodin, Arjang Djamali, Margaret R. Jorgenson, Neetika Garg, Fahad Aziz, Maha A. Mohamed, Didier A. Mandelbrot, Sandesh Parajuli. University of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: BK polyomavirus (BKV) and BKV nephropathy (BKN) are common infections among kidney transplant recipients (KTR). Risk factors and outcomes based on donor characteristics remain largely unknown, although some studies suggest BKV is donor derived. In particular, outcomes based on concordance or discordance for BKV among pairs of deceased donor KTRs receiving sister kidneys are unknown.

Methods: This was a retrospective study including all adult deceased donor KTRs at our center between 01/2014 and 12/2019 in which both donor kidneys were transplanted to two different recipients. Recipient pairs from each donor were divided into three groups based on concordance or discordance for BK viremia between the pair: “no BK-group” if neither KTR developed BKV, “discordant” if one KTR developed BKV but not the other and “concordant” if both KTRs developed BKV. Acute rejection (AR), graft failure and BKN were outcomes of interest.

Results: Of 78 KTRs, 33 (48%) were in no BK-group, 17 (30%) were discordant and 66 (11%) were concordant. Donors in the concordant group were younger, had lower KDPI, were less likely to be DCD, and had lower cPRA. Most of the recipient baseline characteristics were similar in all groups. In a multivariate analysis (MA) adjusting for significant factors, KTRs who had a donor with a higher BMI (HR: 0.57; 95% CI: 0.95-0.99; p = 0.009) were less likely to develop BKV and those who received depleting induction were more likely to develop BKV (HR: 1.77; 95% CI: 1.26-2.51; p = 0.001). There was no difference in the rate of AR, death censored graft failure (DCGF) or BKN among the groups. In MA, concordance was not associated with AR (HR: 0.83; 95% CI: 0.51-1.34; p = 0.45), DCGF (HR: 1.77; 95% CI: 0.42-7.50; p = 0.43) or BKN (HR: 1.02; 95% CI: 0.51-2.03; p = 0.96). By K-M survival analysis, uncensored and DCGF were significantly lower in the concordant group (p = 0.009 and 0.04 respectively), but not affecting between groups that were within one year post-transplant. There was no difference in AR or BKN across the groups.

Conclusions: In this large study of 578 deceased donor KTRs, we identified donor BMI and depleting induction to be associated with BKN. Interestingly, concordance or discordance for BKV was not associated with detrimental outcomes.

PUB275
Risk of Rejection, Graft Failure, and Patient Death After Knee or Hip Replacement Surgery in Kidney Transplant Recipients

Background: There remains a large debate about the timing of hip and knee replacement surgery (joint replacement) in the context of patients with end-stage renal disease (ESRD). Few studies have assessed the surgical complications of knee and hip joint replacement surgery after kidney transplantation; however, there is a need for data regarding risk factors leading to joint-replacement surgery, as well as transplant outcomes. More studies are needed to assess the risk factors of joint replacement on transplanted kidneys in patients with ESRD.

Methods: This was a retrospective study analyzing all adult kidney transplant recipients (KTRs) at our university hospital who underwent hip or knee replacement between 2001 and 2017. Among KTRs with multiple joint replacements, only the first surgery was included. Risk factors for joint replacement and the incidence of rejection and graft survival were compared to controls using incidence density sampling at a 1:3 ratio based on the post-transplant interval.

Results: A total of 101 KTRs underwent joint replacement surgery during the study period. Although we attempted to select controls at a 1:3 ratio, this was not possible in all cases. However for each case, at least one control was selected, resulting in a total of 281 controls. The mean interval from KT to joint replacement was 3.9 ± 3.1 yrs. Patients needing joint replacements were older at the time of KT (56 ± 11.7 vs 50.2 ± 12.9, p < 0.011) and White (94.1% vs 84%, p = 0.01). In regression analysis, only older age was associated with an increased risk of needing joint replacements (HR: 1.04; 95% CI: 1.01-1.06; p = 0.01). In multivariate analyses, the need for replacement was not associated with patient death (HR: 0.79; 95% CI: 0.52-1.18, p = 0.25), death-censored graft failure (HR: 0.87; 95% CI: 0.48-1.56; p = 0.64) or rejection (HR: 1.59; 95% CI: 0.77-3.29; p = 0.21).

Discussion: Our observational study suggests that hip or knee joint replacement after kidney transplantation is not a risk factor for acute rejection, graft failure, or patient death. Further studies are required to determine the risks of complications after joint replacement surgery.

PUB276
Transmitted Renal Hypouricemia in Living Donor Kidney Transplantation: A Case Report and Literature Review
Takamasa Miyauchi,1,2 Malo Teraishita,1 Masatomo Ogota,1 Marie Murata,1 Kiyomi Osako,1 Naohiko Imai,1 Yuko Sakurai,1 Hideo Sasaki,1 Yuko Ohashi,2 Kimiyoshi Ichida,2 Yugo Shibagaki,1 Masahiko Yazawa.1 1Saiti Marianna Ika Daigaku byoin, Kawasaki, Japan; 2Jichi Hattori Clinic, Koto-ku, Japan; Tokyo Yakka Daigaku, Hachioji, Japan

Introduction: Hypouricemia in kidney transplant (KT) recipients is rare since they usually have subnormal kidney function and/or use calcineurin inhibitors. Recently, hypouricemia has gained more interests due to recent progress in understanding of the role of uric acid transporters, and its recognition of renal hypouricemia (RHUC) as a disease, which often compiles kidney stones and exercise-induced acute kidney injury (EIAKI). We report a case of RHUC that developed in a recipient from a living donor with hypouricemia. Besides, we reviewed the previous literature on RHUC among KT recipients/donors for preventing potential complications.

Case Description: A 73-years-old Japanese man underwent KT, and the donor was 58 years-old who used hypouricemia [serum uric acid (S-UA) of 6.6 mg/dL]. Nine months after KT, the recipient’s S-UA was low (1.5 mg/dL) with serum creatinine (S-Cr) of 1.56 mg/dL, and fractional excretion of UA (FEUA) was high (59.7%; normal <10%), indicating RHUC. Regarding the donor’s information, S-Cr, S-UA, and FEUA were 0.95 mg/dL, 1.0 mg/dL, and 54.5%, respectively. To investigate further on the pathogenesis of RHUC in both the recipient and the donor, we performed genetic tests. The donor had a homozygous mutation of W258X in the SLC2A12 gene and the recipient had a wild type of W258X.

Discussion: We eventually found 5 reports and 6 cases of RHUC in KT from a literature review based on past cases reports on MEDLINE. According to the literature review, the incidence of urinary stone and EIAKI in either KT recipients or donors with RHUC were not determined due to a small number of patients in previous studies. However, we should focus on preventing these complications based on the evidence obtained from the general population, since both the recipient and the donor have a single kidney with significant hypouricemia, which potentially can be high risk for these complications. RHUC in donors transmits in recipients, which raise the caution for potential kidney stones or EIAKI in both recipients/donors after KT.

PUB277
Utilization of Donor-Derived Cell-Free DNA and Total Cell-Free DNA to Inform Treatment Decisions in a Pancreas Transplant Recipient with COVID-19 Infection and Rejection
Ty Dunn,1 Kerry Gaj,2 Behdad Besharatian,1 Robert R. Redfield,1 Mary Kaminski,1 Heather Wade,2 Philippe Gauthier.1 1Penn Medicine, Philadelphia, PA; 2Natera, Inc., San Carlos, CA.

Introduction: Donor derived cell-free DNA (dd-cDNA) is an established noninvasive biomarker for immunologic rejection of donor tissue in organ transplant recipients. The Prospera™ test, a SNP-based mmPCR methodology, evaluates dd-cDNA levels as a fraction of total cDNA. Asymptical elevations in total cDNA, as seen in immunologic responses, could affect the assessment of active rejection (AR). dd-cDNA has been analyzed in patients undergoing kidney transplants, however, early data suggests that dd-cDNA behaves similarly following pancreas transplant. Here we present the clinical course of a pancreas transplant recipient with COVID-19 infection for whom, serial dd-cDNA testing was performed.

Case Description: A 51-year-old female received a deceased donor pancreas transplant in August, 2020. The patient was maintained on a triple immunosuppressive (IS) therapy regime, had stable amylase and lipase levels and no episodes of rejection. Six months after KT, the patient received the first dose of a COVID-19 vaccine, and the second dose three weeks later. The patient’s spouse was diagnosed with COVID-19 and soon after, the patient had elevated pancreatic enzymes, 156 and 199 (prior labs 67 and 27) and presented with elevated temperature (100.4 F), cough, fatigue, loss of taste, diarrhea, myalgias and rhinorrhea. The patient was determined to have COVID-19 with a severity score of 2. IS was reduced and monoclonal ab therapy was initiated. dd-cDNA fraction was 1.38%, indicated high-risk for AR, with corresponding total cDNA level elevated 10.2 multiples of the median (MoM). The patient was treated with Methylprednisolone 500 mg and the prednisone tail. Three weeks later, the patient was negative for COVID-19 and IS was resumed. The dd-cDNA fraction at this time was 1.59%, and total cDNA decreased to 1.1 MoM. Subsequent weekly Prospera tests indicated dd-cDNA fractions of 1.03%, 0.54%, and 0.81% with total cDNA levels of 1.4 MoM, 1.3 MoM, and 0.94 MoM. Real-time Prospera Measurement of dd-cDNA can guide IS management in pancreas transplant recipients with COVID-19 undergoing AR. Viral infections and anti-rejection therapies can influence total cDNA. Thus, continued monitoring of both total and dd-cDNA are needed to identify a true response to therapy.
**PUB278**

No Benefit of Prophylactic Surgical Drainage in Combined Liver and Kidney Transplantation: Our Experience

Paolo Vincenzini, Miami Transplant Institute, Liver/GI Transplant Surgery and Kidney/Pancreas Transplant Surgery Miami Transplant Institute, Miami, FL.

**Background:** Contrasting results have emerged from limited studies investigating the role of prophylactic surgical drainage in preventing wound morbidity after liver and kidney transplantation. This retrospective study analyzes the use of surgical drain and the incidence of wound complications in combined liver and kidney transplanted pancreas.

**Methods:** A total of 55 patients aged >18 years were divided into two groups: the drain group (D) (n = 35) and the drain-free group (DF) (n = 20). Discretion to place a drain was based exclusively on surgeon preference. The primary outcome was the development of superficial/deep wound complications during the study follow-up. Secondary outcomes included the development of delayed graft function (DGF) of the transplanted kidney, primary non function (PNF) and early allograft dysfunction (EAD) of the transplanted liver, graft failure, graft and patient survival, overall postoperative morbidity rate and length of hospital stay.

**Results:** With a median follow-up of 14.4 months after transplant, no difference in the incidence of superficial/deep wound complications, except for hematomas, in collections size, intervention rate, PNF, EAD, graft failure and patient survival, was observed between the 2 groups. Significantly lower level of platelets, higher INR values, length of hospital stay, DGF and morbidity rates were reported postoperatively in the D group.

**Conclusions:** Absence of the surgical drain did not appear to adversely affect wound morbidity compared to the prophylactic use of drains in renal transplant patients during CLKTx.

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**PUB280**

Post-Transplant Nephrocalcinosis: A Single-Center Case Study

Aileen Wang, Vivek Charu, Colin R. Lenihan. Stanford University School of Medicine, Stanford, CA.

**Background:** Nephrocalcinosis is characterized by multifocal renal tubular and interstitial findings. Few studies describe the correlates and outcomes of post-transplant nephrocalcinosis. The goal of this study was to describe the characteristics of patients with nephrocalcinosis diagnosed on kidney transplant biopsy at our center.

**Methods:** We searched all adult kidney transplant biopsy reports between January 2010 and May 2021. We extracted demographics and outcomes of post-transplant nephrocalcinosis.

**Results:** Patients characteristics and laboratory findings are shown in Table 1. Mean age was 49±13 years, 69.2% were male and 53.8% Caucasian. Time from transplant to biopsy was 15±18 months. Post-transplant nadir creatinine was 1.25±0.55 mg/dL. Creatinine at the time of biopsy was 1.9±0.72 mg/dL. Creatinine measured at mean of 28 months post-biopsy was 1.89±0.61 mg/dL. Pre- and post-transplant parathyroid hormone enzyme levels were 151±1192 and 264±190 pg/mL, respectively. 4 patients underwent post-transplant parathyroidectomy for a parathyroid adenoma in all cases. 7 and 9 patients were prescribed cinacalcet pre- and post-transplant respectively. Hyperturitoria was found in all 5 patients with available urine studies.

**Conclusions:** Long dialysis vintage, markedly elevated pre-transplant parathyroid hormone level, and cinacalcet use were common in patients with post-transplant nephrocalcinosis. Further study is required to identify risk factors and treatments for post-transplant nephrocalcinosis.

**Funding:** Other NIH Support - National Institute of Allergy and Infectious Diseases, Grant/Award Number 1R25AI147369-01

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**Table 1**

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**PUB279**

Albumin Preceding Simple Plasma Exchange in ABO-Incompatible Kidney Transplantation

Toshitake Naganuma, Yoshiaki Takemoto, Yoshikazu Kuroki, Tomoaki Iwai, Junji Uchida. Department of Urology, Osaka City University Osaka Shiritu Daigaku - Aben Campus, Osaka, Japan.

**Background:** In Japan, where very few deceased donor kidney transplants are performed, approximately 30% of living donor kidney transplants are ABO-incompatible. In these patients, pre-transplant antibody removal by apheresis is generally performed in addition to immunosuppressive therapy. Clinical problems include side effects such as allergic reactions, which are known to frequently occur in recipients who underwent PEx using albumin. Among recipients who underwent PEx using albumin, there were only two sessions in which the patient had side effects including skin rash, redness, and itching, which were frequently observed in recipients who underwent PEx using FFP. The median [IQR] of fibrinogen and factor XIII removal rate was 31.6 [27.5, 42.5] and 31.0 [18.0, 44.4] %.

**Results:** Significant increase in fibrinogen and factor XIII removal rates was observed with albumin, and the incidence of allergic reactions was significantly lower in recipients who underwent PEx using albumin.

**Conclusions:** Albumin is a preferable plasma exchange fluid for ABO-incompatible kidney transplant recipients. Further study is required to identify risk factors and treatments for post-transplant nephrocalcinosis.

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**Adenovirus and Clostridium difficile Coinfection in a Kidney Transplant Recipient**

Katherine Rizzolo, Scott Davis. University of Colorado, Denver, CO.

**Introduction:** Adenovirus infection is associated with AKI (hemorrhagic cystitis, tubulointerstitial nephritis, or obstructive urethritis), fevers, and non-glomerular hematuria. Severe adenovirus infections are rare in solid organ transplants, manifesting within the first year of transplant. In this case, we report fever, AKI, and hematuria one year post kidney transplant due to co-infection of *Clostridium difficile* and adenovirus.

**Case Description:** 65 yo male status post deceased donor kidney transplant one year prior present with five days of diarrhea and fever. Blood work revealed an acute kidney injury (AKI) from a baseline serum creatinine of 1.5 mg/dL to 2.3 mg/dL. He was found to be *Clostridium difficile* toxin positive and started on PO vancomycin and IV fluid. On hospital day 4, he began having high grade fevers to 40°C, worsening creatinine to 5.9 mg/dL, and adenovirus. Severe adenovirus infections are rare in solid organ transplants, manifesting within the first year of transplant. In this case, we report fever, AKI, and hematuria one year post kidney transplant due to co-infection of *Clostridium difficile* and adenovirus.

**Case Description:** 65 yo male status post deceased donor kidney transplant one year prior present with five days of diarrhea and fever. Blood work revealed an acute kidney injury (AKI) from a baseline serum creatinine of 1.5 mg/dL to 2.3 mg/dL. He was found to be *Clostridium difficile* toxin positive and started on PO vancomycin and IV fluid. On hospital day 4, he began having high grade fevers to 40°C, worsening creatinine to 5.9 mg/dL, and adenovirus.
Kidney Transplant in African Americans and Associated Risk of Inferior Allograft Survival

Peter E. Unuakoro, Muhammad S. Yaquh, Asif A. Sharfuddin, Oluwafisayo O. Adebiji, Indiana University School of Medicine, Indianapolis, IN.

Background: Inferior allograft outcomes have been previously reported among African Americans (AA) compared to non-African Americans (non-AA), in the intermediate and long terms. When these inferior allograft outcomes start to occur between AA and non-AA is unclear. Some have attributed loss of Medicare insurance at 3 years post transplantation as responsible in part for these disparities in allograft outcomes between AA and non-AA. Our objective was to compare outcomes after transplantation do AA begin having worse graft/survival outcomes compared to non-AA focusing on the short term as soon as 1 year post transplantation period. We hypothesized that there would be no difference between AA and non-AA in graft survival and function, acute rejection rates, and patient survival 1 year after a kidney transplant.

Methods: This is a single center retrospective cohort. 2069 study participants, mean (SD) age 51 (14.4) years, with 456 (21.8%) participants being AA who received a kidney alone transplant between 2005 - 2016 and were followed up for one year. We compared patient graft survival and function at 1 year, 1-year rates of biopsy-proven acute rejection in AA versus non-AA. We used Cox proportional hazards models to estimate hazard ratios.

Results: No differences were observed in patient survival/surviving graft function. Graft survival with HR of 2.56 (95% CI, 1.03 – 6.35, p=0.04) and one-year acute rejection with HR of 1.73 (95% CI, 1.35 – 2.21, p<0.01) were worse in AA compared to non-AA after adjusting for age, sex, diabetes and donor type.

Conclusions: In this sizeable cohort with ethnic diversity, AA were at higher risk for poor allograft outcomes even in the early post-transplant period compared to non-AA. Further studies evaluating factors including socio-economic determinants of health are needed to mitigate against poorer allograft outcomes.

Comparison of Allograft/Patient Survival at one year between African Americans and non-African Americans

All models were controlled for age at transplantation, sex, diabetes (yes/no) and donor type (living donor versus deceased donor).

Kidney Transplant Patients More Than 1 Year from Transplant: Implications for Clinical Management


Background: Detection of acute rejection in patients more than a year from kidney transplant (KT) relies on monitoring kidney function tests such as serum creatinine (SCr), BUN, protein/creatinine reactions and periodic assessment of donor specific antibody levels. Unfortunately, these metrics are lagging indicators of rejection and other injuries that may contribute to declining allograft function over time. In this setting, regular monitoring of donor-derived cell-free DNA (dd-cfDNA) can enhance the nephrologist’s ability to detect and monitor acute changes in the allograft and to detect early injury caused by immunosuppression (IS) non-adherence. Here we examined the results of the Prospera™ test, a non-invasive single nucleotide polymorphism-based mmPCR methodology to evaluate dd-cfDNA levels, that was performed on patients 1 year after KT.

Methods: We contacted clinics with high-risk Prospera test results (dd-cfDNA >1%) for patients 1-year after KT. Based on the clinical follow-up, we classified the results as rejection, other injury, IS non-adherence or chronically elevated dd-cfDNA for an unknown reason.

Results: We identified 403 patients with Prospera tests performed between 366 and 14,554 days post-KT with a median time of 1445 days. Among test results, the median dd-cfDNA fraction was 2.19% (range, 1.20-73). Clinical follow-up was available for 115 cases with biopsy-matched results available for 24. Biopsy revealed rejection in 33.3% (8/24) of the cases: ABMR (62.5%, 5/8) and TCMR (37.5%, 3/8). An additional 8 biopsies showed pathological findings consistent with other allograft injury including diabetic/hypertensive nephropathy, BK nephropathy, interstitial fibrosis and tubular atrophy and other injury not classified as rejection. Elevated dd-cfDNA test results in patients without biopsy were attributed to IS non-adherence in 4 cases, assessed by the physician, and to viral infection (1 CMV, 3 BK virus) in the remaining 4 cases. These findings resulted in referral to the transplant center for 3 patients, treatment for rejection for 1 patient, and serial testing and increased monitoring for 16 patients.

Conclusions: These findings provide real-world data that supports Prospera’s utility in identifying allografts at high-risk for injury in patients more than 1 year from transplant.
**Figure 1.** Study flowchart of kidney transplant recipients recovered from COVID-19.

**Figure 2.** Brief description of the Study Methods.

**PUB286**

**One-Year Follow-Up of Delayed Graft Function in Renal Transplant Patients Performed in Private Hospitals in the State of México, México**

**Methods:**
- Study population: 28 KT recipients from private hospitals in the State of Mexico.
- Data collection: Clinical records.
- Data analysis: SPSS 11.5.
- Statistical significance: p < 0.05.

**Results:**
- One-year follow-up: 100%.
- Risk factors for ATN-pi:
  - Cold ischemia time: 14.7±4.9 hours vs 5.7±3.8 hours (p = 0.001).
  - Receptor age: Male 10/11 vs 12/13 (p = 0.03).

**Conclusions:**
- ATN-pi was the only cause of GFD.
- Other risk factors found: no other patients met significant risk factors.

**PUB287**

**Challenges Treating Discordant Rejection in Simultaneous Kidney Pancreas Transplant (SPKT)**

**Introduction:**
- Discordant rejection in SPKT is uncommon with limited data on outcomes.
- We present 2 cases of severe discordant acute rejections of the pancreas presenting early post-transplant (PTx).

**Case Description:**
- Patient 1: 46-year-old lady underwent SPKT. 4 months PTx she was admitted, with abdominal pain and elevated pancreatic enzymes. CT showed suggestive of transplant pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. She was re-admitted 10 days later with significant rise in amylase and lipase. Pancreas biopsy showed moderate acute cellular rejection treated with IV Solumedrol and ATG. Patient was readmitted 1 week later with elevated pancreatic enzymes and additional ATG was administered. In the following months while pancreatic enzymes normalized, she developed hyperglycemia needing insulin therapy. 9 months PTx she is on an oral hypoglycemic agent.

- Patient 2: 35-year-old lady underwent SPKT. 9 months PTx she was admitted with fever, elevated pancreatic enzymes elevation and acute kidney injury. Kidney biopsy showed no rejection. CT abdomen showed transplant pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. Patient was readmitted 4 days later with worsening pancreatic enzyme elevation. Pancreas biopsy showed severe acute cellular rejection which was treated with ATG. 12 months PTx, pancreas and kidney allograft function are normal, however, blood sugars are elevated and being monitored without medications.

**Discussion:**
- Treatment of discordant acute pancreas rejection is difficult, particularly with congruent viremia. Large studies assessing allograft and patient outcomes post discordant rejection is needed to better care for this cohort.
Light Chain Deposition Disease (LCDD) Recurrence Post Kidney Transplant

Introduction: Advanced Renal disease from LCDD does benefit from renal transplant but allograft survival may be limited by LCDD recurrence. We report a case to support this

Case Description: 57-yr old male with history of multiple myeloma status post autologous peripheral stem cell transplantaion (PBSCT) and ESRD due to IgG Kappa LCDD who got a deceased donor kidney transplant (DDKT) and developed recurrence of LCDD. Patient evaluated 4 years prior for creatinine 3.43mg/dL, proteinuria 7.4/g/day, kappa light chain(KLC) 118.2mg/dL, lambda light chain(LLC) 13.8mg/dL, K/L ratio 8.5, serum protein electrophoresis (SPEP) with M-spike in gamma region, UPEP showed selective gglomerular proteinuria, urine immunofixation with 2% of total protein being IgG kappa. Kidney biopsy showed diffuse tubular and gglomerular basement membrane staining for kappa light chain (KLC) 3+, weak basement membrane staining for IgG and albumin 1+, moderate -severe fibrosis, negative amyloid. Bone marrow biopsy: 30-40%, hypocellularity, atypical plasmacytosis, plasma cells with CD138 + up to 3% of marrow cellularity, CD56 +, and KLK restricted. Had 3 cycles of chemotherapy with partial response and autologous PBSCT to achieve complete response 1. Two years later, bone marrow and kidney biopsies showed evidence of disease relapse. Had another cycle of chemotherapy and salvage PBSCT, follow up bone marrow biopsy negative for plasma cell abnormality. Started on PD due to worsening renal function. Allograft biopsy 9 months post DDKT done due to elevated serum creatinine and proteinuria showed recurrent LCDD (tubular basement membrane thickening and mesangial expansion with nodular accentuation, 3+ Linear staining for KLC, negative for lambda, focal gglomerular staining for albumin 1+, Electron dense fine granular deposits along gglomerular basement membrane) similar to native kidney biopsy prior to PBSCT. SPEP with M-spike 0.4/g/dL K/L elevated at 11. He was started on chemotherapy for LCDD recurrence. Renal Allograft failed at 10 months post-DDKT and patient returned to Hemodialysis

Discussion: This case illustrates that renal allograft survival is reduced in LCDD patients no matter the treatment used to achieve sustained hematologic response and this supports the need for more studies to establish the pathophysiologic mechanisms underlying LCDD recurrence in renal allograft which may serve as therapeutic targets

Hypoalbuminemia Is a Risk Factor for Invasive Fungal Infections and Worse Outcomes in Infected Kidney Transplant Recipients
Aniruddha Srivastava, Fauzia Osman, Ashad N. Khan, Margaret R. Jorgenson, Neetika Garg, Fahad Aziz, Maha A. Mohamed, Didier A. Mandelbrot, Arjang Djamali, Sandesh Parajuli. University of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Serum albumin is a marker of overall health status. It is unknown if kidney transplant recipients (KTRs) with hypoalbuminemia are at an increased risk of invasive fungal infection (IFI) specifically, blastomycosis, coccidiodosis, histoplasmosis, aspergillosis, and cryptococcosis.

Methods: In this retrospective observational cohort study, all adult KTRs transplanted between 01/01/2001 and 12/31/2017 were included with serum albumin measured 3-6 months before selected IFIs and compared to matched controls using incident density sampling. KTRs were stratified into three pre-infection/albunin levels: normal albumin ≥4.0 g/dL, mild hypoalbuminemia 3.0 ≤< 4.0 g/dL, and significant hypoalbuminemia <3.0 g/dL. Incidence models per 100 person-years and Cox proportional hazards were used to compare outcomes between groups.

Results: 113 KTRs with IFI and 348 controls were included in the study. Mean serum albumin level at the time of IFI was 3.1±0.62 g/dL. The majority of infected KTRs had aspergillosis (48.7%) followed by endemic fungal and cryptococcus infections. Infected KTRs were older at transplant (56±11 vs 53±14 years, p=0.02) with a higher incidence of delayed graft function (23.9% vs 5.8%, p<0.001). Basaline sphincter was more common in those with IFI (55.8% vs 47.4%, p=0.02). Calcium-inhibitor maintenance immunosuppression prevailed overall, but differed (85.9% vs 96.9%, p<0.001). Infected KTRs had lower serum albumin level with 71% normal, 50.4% mild, and 42.5% significant hypoalbuminemia; while in controls 18.7% had normal, 75.9% mild and only 5.5% significant hypoalbuminemia (p<0.001). The incidence rate of IFIs among normal, mild, and significant hypoalbuminemia was 3.6/100, 8.7/100, and 29.3 person-years, respectively. After multivariate analysis, mild hypoalbuminemia (HR: 2.2, 95%CI: 1.02-4.7) and significant hypoalbuminemia (HR: 5.0 95%CI: 2.3-11.2) had a significantly higher risk of IFI than normal albumin. A similar pattern of mortality and graft failure with hypoalbuminemia after IFI was observed.

Conclusions: These results suggest that hypoalbuminemia is associated with an increased risk of IFI as well as subsequent graft loss and mortality.

Incident Fractures in Kidney Transplant Recipients: A Nationwide Cohort Study
Da won Kim,1 Jeesoek Yang,2 Myoung soo Kim,3 Jeong hoon Lee,4 Jin seok Jeon,5 Hye Eun Yoon.1 1Catholic University of Korea, Seoul, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea; 3Yonsei University College of Medicine, Seoul, Republic of Korea; 4Myongji University, Seodaemun-gu, Seoul, Republic of Korea; 5Soonchunhyang University Hospital, Yongsan-gu, Seoul, Republic of Korea.

Background: Increased fracture incidence is a challenging issue among kidney transplantation recipients (KTRs). This study investigated the incidence, location, and predictors of fracture following kidney transplantation (KT).

Methods: Data were obtained from the Korea Organ Transplantation Registry, a nationwide study of KTRs. A total of 5403 KTRs who received KT between January 2014 and June 2019 were included. We estimated incidence rates and risk factors of fracture using Kaplan-Meier method and Cox proportional hazard model.

Results: At median follow-up of 31.6 (18.1 – 46.8) months, 79 patients developed incident fractures. The cumulative incidence of fracture was 2.23% at 5 years. The most frequent locations of fracture were foot (26.3%) and leg (25.0%). Older recipient age [hazard ratio (HR) = 1.038, 95% confidence interval (CI), 1.011 - 1.067; P = 0.007] and diabetes mellitus (HR = 2.404, 95% CI, 1.383 – 4.180; P = 0.002) at baseline were associated with higher risks for fracture after KT, while the use of anti-thymocyte globulin as induction therapy (HR = 0.233, 95% CI, 0.073 – 0.748; P = 0.014) and higher calcium * phosphorous product at 6 months post-transplantation (HR = 0.950, 95% CI, 0.906 – 0.995; P = 0.032) were associated with a lower risk of fracture.

Conclusions: The first 5 years after KT were associated with risks of peripheral skeleton fractures. Recipients’ age, diabetes mellitus, induction therapy, and post-transplant calcium/phosphorus interaction may explain the risk. These results define the need of further studies to evaluate the reason for the fracture risks of KTRs.

Outcome of 313 Czech Patients with IgA Nephropathy After Renal Transplantation
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Introduction: Advanced Renal disease from LCDD does benefit from renal transplantation. Recurrence of LCDD is a risk factor for graft failure. Risk factors for a bad outcome of graft failure are gender, age, diabetes mellitus, induction therapy, and post-transplant calcium/phosphorus interaction may explain the risk.

Methods: We evaluated clinical parameters and pathological findings at the time of biopsy of native kidney and after kidney transplant in 313 Czech patients with IgAN during the follow up of 26 years. Logistic regression model, hypothesis test on binomial distribution and Kaplan-Meier survival curves were used for statistical analysis.

Results: Histologically verified recurrence of IgAN was confirmed in 23 individuals (46.0%) of the total number of 50 (16.0 %) patients with IgAN with irreversible graft failure. Microscopic hematuria was detected just in 31 patients (62.0%) with graft failure. 10-years renal survival was unfavourable in patients with histologically confirmed recurrence of IgAN and microscopic hematuria in comparison with patients with recurrence of IgAN without microscopic hematuria. Using hierarchical clustering method patients with graft failure were divided into two groups according to the time from kidney transplant to graft failure (11.2 versus 6.1 years) which excellently correlated with the distribution of two groups based on the time from the renal biopsy of native kidney to end stage renal disease (5.9 versus 0.4 years). Body mass index, proteinuria, microscopic hematuria, histological evaluation of fibrosis and crescents at the time of renal biopsy of native kidney were confirmed for the differentiation into two groups.

Conclusions: The presence of microscopic hematuria together with histologically verified recurrence of IgAN were confirmed to be unfavourable predictors of renal survival in our cohort of 313 Czech patients after kidney transplant (P<0.001). Higher age of donor kidney transplant, histological verified recurrence of IgAN, antibody mediated rejection and the onset of microscopic hematuria and proteinuria till one year after kidney transplantation were confirmed for a significantly worse graft survival in multivariate Cox regression analysis in patients with original diagnosis of IgAN in native kidney biopsy.
**PUB292**

**Symptoms and Occurrence of Hepatitis E in Solid-Organ Recipients: A Single-Center Experience of the Last Five Years**

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Nephrology department, Transplantation Center Ludwig-Maximilians-University München, Medizinische Fakultät, München, Germany.

**Background:** The Hepatitis E virus (HEV) can be found worldwide and the transmission is mainly fecal-oral. In Germany, transfection occurs especially from pork or beef, where genotype 3 is predominant. While most infections are asymptomatic, under immunosuppressive therapy a chronic (and fatal) course of Hepatitis E is possible. Regular testing is often missing due to lack of experience. Therefore, we retrospectively evaluated all solid-organ transplant patients in our tertiary care center with a positive diagnosis of Hepatitis E in the last five years.

**Methods:** All solid-organ recipients with positive HEV-RNA replication in the blood in the last 5 years were retrospectively analysed regarding disease manifestation, immunosuppressive therapy, and course of HEV infection. HEV-IgG or IgM alone were not sufficient for diagnosis.

**Results:** From 2015 to 2020 14 solid-organ transplant patients (4x kidney, 5x heart, 4x liver, 1x lung) were diagnosed with HEV in our center. All patients showed elevated transaminases before diagnosis. In total 3 patients experienced abdominal pain, two presenting with acute liver failure. Overall, HEV infection occurred after a median of 8.6 years after transplant, however 3 patients developed HEV within the first year after transplantation. The transplantation path remained uncertain in all cases. Blood transfusions were never associated, contaminated and/or undercooked meat was the most likely cause, especially as none of the patients were vegetarian. Regarding immunosuppressive therapy, 92 % (N=13) had a tacrolimus based regimen combined with either mycophenolic acid or m-Tor inhibitor. No significant differences between the two could be found. 10 out of 14 patients were treated with Ribavirin because of either persistent HEV-RNA or because of the severe course of the disease. In 4 patients HEV infection disappeared without specific treatment due to the reduction of immunosuppressive therapy. One patient developed a chronic HEV infection, which resolved after Ribavirin therapy.

**Conclusions:** HEV is a common cause of elevated transaminases in solid-organ recipients and should be considered for differential diagnosis. Therefore, we suggest a more precise measurement – even years after transplantation – regarding cooking rules.

**PUB293**

**Vancomycin Nephrotoxicity Causing Renal Transplant AKI**

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**Introduction:** Nephrotoxicity is a rather frequent side effect of vancomycin treatment. Attributes of vancomycin nephrotoxicity (VN) are well documented including high fluid losses and global renal morphologic changes. However, VN has not been documented as the cause of acute kidney injury in the renal transplant setting.

**Case Description:** We herein reported the first three such cases. In each of these cases acute kidney injury developed concurrently with vancomycin treatment and resolved after its cessation. As compared with the general population VN in the renal transplant setting displayed some unusual clinical behaviors. Its development was rather capricious, being noted in some treatment episode, but not others even in the same patient. Acute kidney injury developed gradually in conjunction with a protracted vancomycin treatment, in contrast to a precipitous course in the non-transplant setting. However, renal transplant biopsies showed typical features of VN in each case.

**Discussion:** VN is an exceptional but now well documented cause of acute kidney injury in renal transplant recipients. VN in this setting may display some atypical features.

**PUB294**

**A Qualitative Exploration of Patient-Provider Communication Challenges After a Kidney Transplant**

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**Background:** Kidney transplantation is a life-altering treatment, but symptoms and drug effects prompt for many patients post-transplant. Effective communication with the healthcare team (HT) is key to address these, yet research shows patients find that challenging. Ineffective communication may lead to inadequate assessment and management of symptoms. Although communication is among patients’ top research priorities, less than 5% of articles in the two leading transplant journals address it. To fill this gap, we conducted a qualitative exploration of communication challenges from recipients’ perspective.

**Methods:** Within a larger study, we used Qualitative Description methodology to understand the quality of communication between patients and HT post-transplant. Purposive recruitment was done via flyers (Jun-Dec 2020). Patients with significant cognitive impairment or insufficient English were excluded. In-depth, semi-structured, individual interviews were recorded and transcribed verbatim. Directed content analysis framed the iterative development of codes.

**Results:** 7 recipients (4 males, ages 51-75, 4-15.5 years post-transplant) and 1 caregiver participated. Findings indicate a range of experiences, from regular contact with HCT to infrequent. While some proactively initiate communication-in-between clinical visits. Compared to pre-transplant care, communication was less frequent and many patients felt isolated, making it difficult for them to know where and how to seek information and support. Instead, patients relied on searching for information online, visiting family doctors or the emergency room. Some used phone/voicemail to reach HCT, but these were not always timely or efficient. Patients also raised the need for HCT to consider the uniqueness of each patient and their broader context, in addition to quantitative measures, in assessing their health. The diverse communication experiences also relate to patients’ comfort with self-advocacy. While some proactively initiate conversation, others are more reserved.

**Conclusions:** Communication challenges between kidney transplant recipients and HCT contribute to feelings of isolation and difficulties navigating post-transplant life. Tailoring communication to individual preferences may improve patient-centered care.

**PUB295**

**CMV-Associated Thrombosis in a Kidney Transplant Recipient**

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**Introduction:** Cytomegalovirus (CMV) infection is a common infectious complication after kidney transplantation. Indirect effects of CMV infection include an increased risk of secondary infections, increased risk of acute rejection and chronic allograft dysfunction. CMV is well known that CMV may lead to the risk of venous and arterial thrombosis. Here we present a case of acute deep venous thromboembolism associated with acute CMV disease in a kidney transplant recipient.

**Case Description:** A 64 year old male presented with 4 weeks of sore throat, cough, subjective fever, fatigue, and palpitations. 3 weeks prior, he presented to an outside hospital with flu-like symptoms and complaints of right calf pain. Imaging showed the right leg with totally thrombosed posterior tibial and peroneal veins as well as acute partially thrombosed popliteal vein. The patient was subsequently admitted to the hospital and found with a CMV PCR of 35,900 IU/ml, after which he underwent an esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies confirming CMV in the lower esophagus consistent with CMV esophagitis. IV ganciclovir treatment was initiated with appropriate response seen.

**Conclusion:** CMV belongs to the herpesvirus family that establishes latent infection following a primary infection. For patients who are CMV seropositive, the risk of CMV reactivation is highest in the setting of systemic immunosuppression. CMV infections may present with a wide array of syndromes ranging from meningoencephalitis to enteritis/collitis and hepatitis. In addition, CMV infection has been associated with thromboembolic events. Kidney transplant recipients show a high prevalence of thrombotic events compared with the general population. In short, acute CMV infection should be considered as a risk factor for venous thromboembolism. Therefore, diagnosis of acute CMV infection in patients with an acute thrombosis should redefine the thrombotic event as provoked rather than unprovoked, limiting the duration of anticoagulation treatment.

**PUB296**

**Comparison of the Efficacy and Safety Between Anti-Thymocyte Globulin (ATG) and Basiliximab in Deceased Donor Kidney Transplantation: A Multicenter Cohort Study**

Suveen Hong, Chul Woo Yang, Byung ha Chung, Woo Yeong Park, Kyubok Jin, The Catholic University of Korea, Seoul St. Mary’s Hospital, Seoul, Seoul, Republic of Korea; The Catholic University of Korea, Uijeonbu St.Mary’s Hospital, Uijeonbu, Gyeounggido, Republic of Korea; Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea.

**Background:** Induction immunosuppressant is decided upon the condition of deceased donors and recipients in deceased donor transplantation (DDKTX). Although anti-thymocyte globulin (ATG) is preferred in immunologically high risk patients, there has no clear evidences for the efficacy and safety of induction agent in DDKTX. This study aims to compare the efficacy and safety between ATG and basiliximab (BSX) based on donor characteristics in DDKTX.

**Methods:** A total of 724 kidney transplant recipients (KTRs) from 3 transplant centers were enrolled and ATG-DDKTX group was 252 and BSX-DDKTX group was 472. We investigated the impact of induction therapy based on donor age of 60, donor kidney with acute kidney injury (AKI) and kidney donor profile index (KDP1) score of 65% on post-transplant clinical outcomes in delayed graft function (DDF), acute rejection (AR), infectious complications, allograft and patient survivals.

**Results:** ATG-DDKTX group had poor donor condition and highly sensitized recipients than BSX-DDKTX group. DGF did not show statistically significant differences among induction agent in terms of elderly young donor, AKI/non-AKI, and high-KDP1/low-KDP1 subgroups. Acute rejection and infection rate did not show meaningful differences. Death-censored allograft survival and patient survival rate between induction agents were also statistically irrelevant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

847
Conclusions: Our results suggest that though ATG was more frequently applied to poorer donor condition and highly sensitized recipients, ATG was not inferior to BSX not only in aspect of survival rate but also DGF, AR and infection aspects. Therefore, as an induction agent, ATG should be considered in preference to BSX, especially in high-risk DDRT.

Funding: Government Support - Non-U.S.

Table 5: Risk factors for allograft failure in deceased donor kidney transplantation

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% C.I.)</th>
<th>P</th>
<th>Adjusted HR* (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy</td>
<td>1.229 (0.717–2.091)</td>
<td>0.400</td>
<td>0.713 (0.369–1.383)</td>
<td>0.322</td>
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<tr>
<td>Transplant years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2016–2012</td>
<td>0.756 (0.473–1.234)</td>
<td>0.206</td>
<td>0.015 (0.005–0.268)</td>
<td>0.032</td>
</tr>
<tr>
<td>2013–2019</td>
<td>0.440 (0.300–0.684)</td>
<td>0.200</td>
<td>0.124 (0.045–0.350)</td>
<td>0.321</td>
</tr>
</tbody>
</table>

PUB297

Longitudinal Urinary Inflammatory Profile During Renal Transplantation
Elizabeth Spiwak, Corina Nailescu, Andrew L. Schwaderer. Indiana University School of Medicine, Indianapolis, IN.

Background: In the year 2020, more than 5,000 living donor kidney transplants were performed in the United States. Kidney transplant recipients are subjected to several types of immunosuppressants in order to prevent rejection of the graft. Over-immunosuppression increases the risk of infectious complications and these patients require a delicate balance. Inflammatory profiles from the urine can help identify which biomarkers may guide clinicians in balancing over vs. under-immunosuppression.

Methods: Urine samples were obtained from 12 kidney donor-recipient pairs at a pre-operative visit ~1 week prior to or at time of transplant and then for the recipients, ~3 months following transplantation. The urine samples were analyzed using inflammatory urine biomarker profiles (Mesoscale Discovery). Urine levels were then normalized to urine creatinine values. Differences were noted between groups using the mixed-measures ANOVA, corrected for multiple comparisons with the Tukey test to get adjusted p-values.

Results: Results are presented in the figure, but it was identified that eotaxin urine levels were higher in post-transplant samples compared to donor samples; interleukin-6 levels were higher in pre-transplant samples compared to both donors and post-transplant samples; GM-CSF levels were higher in pre-transplant samples compared to their donors; and interleukin-6 levels were higher in pre-transplant samples compared to their post-transplant samples.

Conclusions: The urine inflammatory profile evolves over the transplant course between donors, pre-transplant recipients and transplant recipients. Although the transplant itself is typically accepted as a pro-inflammatory event, levels of biomarkers in the urine tend to decrease post-transplant. Immunosuppression regimens may influence inflammatory profiles and warrant further investigation.

Funding: NIDDK Support

PUB298

A Study of Outcomes of Renal Transplantation from Deceased Donors in a Tertiary Care Centre from Southern India
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Background: In India, there are large number of end stage renal disease patients awaiting renal transplantation. Deceased donor renal transplantation (DDRT) is one possible solution to this. So this study aimed to determine the outcomes of DDRT.

Methods: Total 126 DDRT recipients in a tertiary care hospital in southern India, between 2013 and 2020 were taken in to the study and the outcomes were retrospectively analysed.

Results: Out of 339 renal transplants, 126(37%) were DDRT in the study period. Mean age at transplant was 58.3 years. 77.7% were males and 22.3% were females. 73.8% patients received basiliximab, 26.2% received antithymocyte globulin for induction. Steroids, calcineurine inhibitors and mycophenolate mofetil were used for maintenance immunosuppression. Over a mean follow up of 3.6 years, patient and graft survival rates were 85% and 92.6%, respectively, with a median serum creatine of 1.32 mg/dl. The incidence of delayed graft function (DGF) was 54.3%. The incidence of slow graft function was 33.4%. The incidence of immediate graft function was 12.3%. Prolonged cold ischaemia time was risk factor for DGF. Mean cold ischemia time was 4.2 hours.

Conclusions: Outcomes of DDRT showed successful results. So DDRT has a potential to expand donor pool and shorten the waiting list for renal transplantation. Increasing public awareness and good communication and a well trained team of transplant coordinators can help in improving the number of organ donations.

PUB299

Pressure Natriuresis and Diuresis Are Differentially Regulated Depending on Age and Sex
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Background: The renal capacity for handling salt and water is linked to hypertension. This study aimed to clarify the sex- and age-related natriuretic and diuretic differences in blood pressure (BP) regulation.

Methods: We analyzed two datasets: one from the E-SPECIAL trial, which evaluated the effect of a low-salt diet (LSD) on lowering albuminuria in 235 patients with nondiabetic chronic kidney disease, and the other from the Korean Genome and Epidemiology Study (KoGES), including 4,937 subjects.

Results: In the E-SPECIAL trial, BP was lower in premenopausal women (Pre) than in younger men (Y), and the gap disappeared between postmenopausal women (Post) and older men (O). LSD decreased urine sodium in Y, Post, and O but did not mitigate urine sodium in Pre. A positive correlation between BP and urine sodium was
observed only in the younger groups (Pre, Y). Urine volume was greater in Pre than in Y. Sodium concentration was also higher in Pre compared to Y. Urine sodium was positively correlated with BP in Pre and negatively associated with BP in other groups. Urine volume and sodium were the most decisive factors for predicting BP in Pre. In the KoGES, BP was lowest in Pre. Urine sodium increased in Pre compared with Post, although sodium intake was not different. The correlation between BP and urine sodium augmented in younger groups (Pre, Y).

Conclusions: The pressure-natriuretic and pressure-diuretic responses were well conserved in Pre and mitigated in Post. Augmented natriuresis and diuresis might contribute to lower BP in Pre.

PUB300
Misoprostol-Induced Pulmonary Edema in a Pregnant Woman with ESKD Undergoing Induction of Labor Following SARS-CoV-2 Infection
Kelly H. Beers, Swati Mehta, Geovani Padow. Albany Medical College, Albany, NY.

Introduction: Misoprostol can induce pulmonary edema in patients with end stage kidney disease (ESKD) undergoing induction of labor (IOL). Careful monitoring and interdisciplinary care is required in these complicated patients with tenuous respiratory status. We present a case of misoprostol-induced pulmonary edema in a pregnant woman with ESKD requiring hemodialysis (HD) who may have been at higher risk of adverse effects due to recent SARS CoV-2 infection.

Case Description: A 21-year-old woman at 34 weeks, 6 days gestation in her first pregnancy and ESKD due to IgA nephropathy on home hemodialysis (HHD) was admitted for IOL. She had been hospitalized at 21 weeks gestation with severe SARS CoV-2 infection requiring ICU stay. She recovered and was discharged on HHD 6 hours, 6 days weekly. She required 2L supplemental oxygen upon discharge for a total of 7 weeks. Her BUN was maintained < 35mg/dl throughout her pregnancy. Prior to IOL, patient was euvolmic with oxygen saturation of 96% on room air, and patient was at her dry weight. IOL was initiated with two doses of vaginal misoprostol, 25mg per dose, first dose at 8:37 PM then another at 12:38 AM. At 3AM she developed flash pulmonary edema. Her oxygen saturation dropped to 90% and B lines were seen in the apex of both lungs on point of care ultrasound. No clinical or laboratory signs of pre-eclampsia were found. Patient required urgent dialysis with 2L of fluid removal while she was in early labor, with resolution of symptoms. Given her tenuous fluid status, it was decided to perform primary cesarean section, which resulted in the birth of a healthy infant.

Discussion: Misoprostol has been identified as a possible cause of pulmonary edema in at least two cases of otherwise healthy asymptomatic patients. This is first report of misoprostol causing flash pulmonary edema in a patient with ESKD. Other prostaglandin analogues have been reported to cause pulmonary edema, and the FDA lists edema and increased pulmonary edema as side effects for oral misoprostol. Misoprostol has been identified as a possible cause of pulmonary edema in patients with ESKD undergoing induction of labor (IOL). Careful monitoring and interdisciplinary care is required in these complicated patients with tenuous respiratory status. We present a case of misoprostol-induced pulmonary edema in a pregnant woman with ESKD requiring hemodialysis (HD) who may have been at higher risk of adverse effects due to recent SARS CoV-2 infection.

PUB301
Predictors of Readmission in Patients with Advanced CKD and Colon Cancer: A Nationwide Analysis
Vincent E. Prado,1 Miguel Salazar.2 University of Cincinnati, Cincinnati, OH; 2Cleveland Clinic, Cleveland, OH.

Background: It is well-documented that chronic kidney disease (CKD) and colorectal cancer (CRC) have an almost reciprocal effect, with CKD associated with development of CRC and vice versa. We attempt to explore predictors that increase the risk for 30-day readmission rates in patients with CRC and concomitant CKD.

Methods: A retrospective study of the 2017 National Readmission Database of adult patients readmitted within 30 days after an index admission for CRC with a concomitant diagnosis of CKD 4 and greater. We aim to identify 30-day readmission rate, mortality, healthcare related utilization resources, and independent predictors of readmission.

Results: A total of 5,678 patients with CRC were admitted with a diagnosis of CRC. The 30-day readmission rate was 28.3%. Main causes for readmission were sepsis, acute kidney failure (AKI), recurrent malignant or metastatic disease and pericarditis. Readmitted patients were more likely to be female (39.9% vs 37.1%; P<0.05), obese (15.2% vs 11.8%; P<0.01), diabetes (37.6% vs 29.4%; P<0.01) and leuko (12.4% vs 8.7%; P<0.01). Readmission was associated with higher in-hospital mortality rate (1.5% vs. 0.1%; P<0.01), hypertension (2.2% vs 4%; P<0.01), and hemodialysis requirement (32.7% vs 36.4%; P=0.03). The total health care in-hospital economic burden of readmission was $104 million in total charges and $25.1 million in total costs. Independent predictors of readmission were prolonged length of stay, pleural effusion, and alcohol abuse. Factors preventative of readmission were younger age and disposition to a skilled nursing facility.

Conclusions: Readmissions in patients with CRC and comorbid advance stages of CKD (4 & 5) is associated with high morbidity and health care burden. Through this study, we identified risk factors that can be targeted to help reduce this burden. Controlling these factors could help reduce readmission rates and thus reduce morbidity and mortality. Similarly, focus on proper disposition planning can greatly improve outcomes.

PUB302
Urinary Dickkopf-3 (Dkk3) Uncovers Unapparent Progressive Kidney Injury in Patients with Chronic Obstructive Pulmonary Disease: An Etiological Study and Experimental Validation
Stefan J. Shunk, Danilo Fiser, Thimoteus Speer. Universitätsklinikum des Saarlandes and Medizinische Fakultät der Universität des Saarlandes, Homburg, Germany.

Background: Chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) represent global public health problems with high disease-related morbidity and mortality. However, the interaction between both diseases remains unclear.

Methods: In a novel murine model, cigarette smoke (CS)-induced lung injury was combined with a CKD model (CS-CKD model). In 2,314 patients of the prospective multi-center COSYCONET study, urine Dickkopf-3 (Dkk3), a renal tubular stress marker, was quantified. The association between urinary Dkk3 and trajectories of FEV1, and estimated glomerular filtration rate (eGFR), exercise capacity, risk of exacerbation, and mortality was determined (follow-up 37.1 months).

Results: In the CS-CKD model, CKD was associated with higher systemic and pulmonary inflammation, and the combination of CKD and CS significantly aggravated kidney inflammation as well as fibrosis and increased renal expression of Dkk3. Abrogation of Dkk3 attenuated kidney injury and pulmonary inflammation alike. In COPD patients, higher urinary Dkk3 was associated with rapidly declining FEV1 (OR 3.36, P<0.0001), higher risk for exacerbation, lower 6-minute walking distance, and higher all-cause mortality (HR 1.49, P=0.015). Importantly, higher urinary Dkk3 was also associated with declining eGFR during follow-up (OR 2.23, P=0.0005). Neither eGFR nor proteinuria were associated with lung or kidney dysfunction during follow-up.

Conclusions: In summary, the present study identified a strong pathophysiological link between lung and kidney dysfunction, which is at least partially mediated by Dkk3. Urinary Dkk3 allows identification of COPD patients at increased risk for deteriorating pulmonary and kidney function as well as adverse outcomes. These patients might particularly benefit from preventive therapeutic strategies as a personalized-medicine approach.

PUB303
Outpatient Treatment Patterns of Hyperkalemia in the United States: The Design and Initial Findings from ZORA, an Observational Study
Eva Lesén,1 Abiy Agiro,2 Alastair Allum,3 Jonatan Hedberg,1 Mina Khهزian,1 Krister Järbrink,1 1AstraZeneca, Gothenburg, Sweden; 2AstraZeneca US, Wilmington, DE; 3AstraZeneca, Cambridge, United Kingdom.

Background: Hyperkalemia (HK) is a potentially life-threatening disorder due to alterations in cardiac conduction, which may result in arrhythmias and sudden death. Potassium binders is a key pillar in the outpatient treatment of HK, but conventional binders, including sodium polystyrene sulfonate (SPS), are generally poorly tolerated, lack palatability and have limited long-term efficacy – with suboptimal use as a consequence. New potassium binders (patiromer and sodium zirconium cyclosilicate [SZC]) with a more beneficial tolerability profile have become available, but contemporary real-world evidence on outpatient treatment patterns including these new therapeutic options is scarce.

Purpose: To describe the characteristics and treatment patterns among patients with outpatient potassium binder treatment in the US.

Methods: This is an observational study including patients who filled an outpatient prescription for SPS, patiromer or SZC between 1 Jan 2018 and 30 Jun 2020, as identified in HealthVerity claims linked with Quest Diagnostics laboratory data. Patient characteristics and binder treatment patterns will be described using standard descriptive statistics and survival analysis.

Results: The data set includes a random sample of 20,000 patients with a filled prescription for SPS, and approximately 20,000 patients with a filled prescription for a new binder (patiromer or SZC), over a data capture period of 30 months for patiromer and 12 months for SZC. Analyses on patient characteristics (such as demographics, HK severity, comorbidities, treatment history etc.) and their associations with outpatient treatment choice, as well as binder treatment patterns and trends over time, are ongoing and will be presented.

Conclusions: This study will identify important insights into the characteristics and binder treatment patterns among US patients with HK, and provide useful guidance to improve adherence to guidelines and optimize patient care.

Funding: Commercial Support - AstraZeneca
Results: Preliminary results show that the prevalence of CKD stages 1–5 is projected to increase from 13.35% to 14.22% in Canada, from 13.48% to 13.98% in the UK, and from 14.88% to 15.57% in the US from 2021 to 2026 (Table). The number of patients receiving RRT annually is projected to increase from 42,064 to 47,582 in Canada, from 69,796 to 75,051 in the UK, and from 797,638 to 823,050 in the US, between 2021 and 2026 (Table).

Conclusions: Inside CKD projects that the prevalence of CKD will continue to rise in Canada, the UK and the US over the period 2021–2026 with a corresponding increase in the annual RRT burden. These data demonstrate that CKD continues to pose a significant global challenge to public health and demonstrates the continued need for national policies aimed at early intervention.

Funding: Commercial Support - AstraZeneca

Projected increase in CKD stages 1–5 (including undiagnosed) and RRT from 2021 to 2026

*Percentages expressed as a proportion of total projected country population
Risk of Pulmonary Emboli in Patients with Renal Failure  
Ahsibek Sul, Arsalan Zahid, Jonathan Paul, Stephanie Besser, Mary S. Hammes. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: There are 2 million cases of deep vein thrombosis and 200,000 deaths due to pulmonary emboli (PE) each year in US. The LITE study showed a relative risk of 2.1 (95% CI 1.5-3.0) for venous thromboembolic events in advanced renal failure with limitations as patients with ESRD were not included, renal function at time of event was not defined, and no definition or clot burden or cardiac function. The objective of the current study was to characterize the thrombotic event and details of cardiac function in patients who develop PE, stratifying for renal failure along with determination if demographic data or medical history can predict the outcome or severity of a PE.

Methods: This was a retrospective review conducted at a single-center in an urban community. Charts were reviewed from patients who were referred to the Pulmonary Emboli Response Team (PERT) for treatment of a PE. Demographic data, medical history, and labs including serologic markers of renal and cardiac were reviewed. Patients were stratified based on renal function. Controls had an eGFR > 60 ml/min as compared to patients with AKI or a history of CKD. PE severity was defined using 2019 ESC guidelines with the most severe classification (4) having hemorrhagic instability. Cardiac parameters reviewed included echocardiograms and CT scans.

Results: Charts were reviewed for 170 patients who were admitted for a PE with PERT team activation between 2017 through 2020. There were 45 included patients with AKI, 37 with Stage 3 CKD, 20 with Stage 4-6 CKD, 69 in the control group defined as a eGFR > 60 ml/min. The control group was younger with a lower incidence of coronary artery disease and hypertension (p <0.05). Mortality associated with a PE was stratified for renal function with a higher in-hospital mortality in patents with AKI and advanced CKD when compared to controls (p=0.052). Logistic regression was performed to ascertain the relationship of the severity of the PE and renal failure with an OR 2.92 SE 1.54 (95% CI 2.1-4.0) p=0.003. Patients had a 9-fold increased risk of PE Severity Class 4 if they had renal failure when compared to controls.

Conclusions: Patients with advanced CKD or AKI tend to have a higher PE severity with greater in-hospital mortality. Efforts to triage and aggressively treat patients with renal failure who present with PE may improve outcomes.

Effects of Air Pollutants on Mortality of Patients with CKD Living in Green Spaces in Seoul, Korea: A Large Observational Study  
Jiyun Jung,1 Jangwook Lee,1 Yong Chul Kim,1 Jung Pyo Lee,2 Yun Su Kim,2 Sung Joon Shin,3 Jae Yuon Park,1 Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Owing to increasing air pollution, the association between green spaces and health outcomes has become a global health concern. The relationship between air pollution and the survival of patients with chronic kidney disease while considering residential greenness remains to be elucidated.

Methods: Time-varying survival analysis was conducted to investigate the association between long-term exposure to air pollutants (PM2.5, PM10, NO2, SO2, CO, and O3) and mortality in 29 602 chronic kidney disease patients living in residential environments within 500 m and high green infrastructure. Low and high green infrastructure was defined as continuous (0.3, 0.35, and 0.4) and percentilie (50%, 75%, and 90%) thresholds using satellite data derived average normalized difference vegetation index within 250 m and 1250 m around the residence.

Results: During the average 6.14 ± 3.96 observation period, 3 863 (14%) deaths occurred. The effect of exposure to air pollution on mortality was stronger in the low index group compared to the high index group. Particularly, SO2 was significantly associated with increased mortality risk in the low index group regardless of the threshold. Conclusion: Results were observed in the co-pollutant models.

Conclusions: Exposure to high greenness significantly reduced the mortality risk associated with air pollution. Our results emphasize the need for creating environmental infrastructure considering green spaces.

Impact of Inpatient Educational Programs on Mortality After the Introduction of Dialysis Therapy  
Keisuke Yoshida,1 Yohei Kita,2 Wei Han,3 Sayaka Shimizu,4 Yugo Shibaegaki,2 Tsutomu Sakurada,1sei Marianna Ika Daigaku,2 Kawasaki, Japan; 3Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan.

Background: Although inpatient educational programs (IEPs) for non-dialysis-dependent chronic kidney disease patients (CKD) have been reported to slow disease progression, its effect on prognosis after the introduction of dialysis therapy is unclear.

Methods: Consecutive patients who started dialysis therapy between January 1, 2011 and December 31, 2018 were included in this study. The patients were divided into two groups according to whether or not they received IEPs before dialysis introduction, and their background characteristics were compared. The survival rate for each group was calculated using the Kaplan-Meier method and compared by the log-rank test. Furthermore, the hazard ratio (HR) adjusted for confounding factors associated with mortality (age, sex, BMI, CCI, eGFR, albumin, ADL, smoking, welfare patient and eGFR at hospitalization) was calculated using a Cox regression analysis.

Results: Of the 489 subjects (mean age 68 years, 71.0% male), 129 patients (26.4%) received IEP. Compared with the non-IEP group, the IEP group had higher serum albumin (p <0.001) and lower total cholesterol levels (p =0.0078), and the proportion of patients with cardiovascular disease in their daily living activities was high (p = 0.005). The median observation period was 3.8 years, and 153 people (31.3%) died. The 5-year survival rates[1] [A2] [A3] were 81.0% and 61.4% in the IEP and non-IEP groups, respectively (p = 0.015). From the Cox regression analysis,[A4] [A5] [A6] the HR for the IEP group was 0.56 (95% CI 0.36-0.88).

Conclusions: IEPs for CKD patients were associated with a more favorable prognosis after initiation of dialysis.

The Prevalence of Adverse Childhood Experiences in Adults with CKD  
Kira Clark, Amira Al-Uzri. Oregon Health & Science University, Portland, OR.

Background: Adverse childhood experiences (ACE) are traumatic events of physical and emotional neglect and abuse, sexual abuse, household dysfunction, caregiver instability, community violence, and collective trauma. Previous research shows the prevalence of ACEs is higher in people with chronic disease, but limited data is available on the prevalence of ACEs in people experiencing chronic kidney disease (CKD).

Methods: This case-control study used the Adverse Childhood Experiences International Questionnaire to compare the ACE prevalence of people diagnosed with CKD (case) to people without CKD (control). ACE scores consisted of 13 trauma subtypes and were coded on a scale from 0-13 for an overall score. Fisher’s exact test determined the difference between groups within a 95% confidence interval. Logistic regression examined group differences for each ACE sub-type and adjusted for sociodemographic confounders.

Results: The analysis included 34 people with CKD and 29 controls. Subjects were predominantly female (66.7%), white (84.1%), had a college degree (73.0%), were employed full-time (54.0%), and had a M age of 36.1 (± 8.6) years old. Subjects with CKD were diagnosed around 25.5 (± 13.6) years old with a mean eGFR of 38.5ml/min/1.73m2. ACE scores for CKD (M = 6.7, SD = 3.2) compared to control group (M = 5.0, SD = 3.0) demonstrated significantly higher ACE scores, (61) = 2.4, p = 0.02. People with CKD had a higher prevalence in 11 of the 13 ACE trauma sub-types with the highest reported categories including bullying (91.2%), emotional abuse (82.4%), physical abuse (70.6%), household violence (70.3%), and caregiver mental illness (64.7%). Statistically significant (p <0.05) differences in prevalence occurred with exposure to emotional neglect, caregiver mental illness, and sexual abuse. Odds ratios for having a CKD diagnosis were significant (p <.05) for emotional neglect (OR; 8.84), caregiver mental illness (OR; 4.81), sexual abuse (OR; 4.52), and bullying (OR; 5.55).

Conclusions: This pilot research indicates that adults with CKD experienced every trauma sub-type of ACE and at higher frequencies than a control population. Cumulative exposure to ACEs and experiencing specific trauma sub-types increased the odds of having a CKD diagnosis. Further research is needed to explore how ACEs affect disease occurrence and management of people with CKD.

 Increased Mortality due to Uranium-Associated Renal Disease Has Not Been Observed in Uranium Workers: A Meta-Analysis  
Greg Shoup, Donald A. Mölony. The University of Texas Health Science Center at Houston John H and Katherine G McGovern Medical School, Houston, TX.

Background: Studies in animal and human populations have suggested nephrotoxic effects of uranium exposure, but little statistical synthesis of the data has been done. This study aims to update and expand on existing meta – analyses of mortality due to renal disease by evaluating multiple uranium – exposed populations. This study also aims to further evaluate the effect of uranium exposure on renal biomarkers.

Methods: PubMed, Embase, Web of Science, and Trip Database were searched through September 2020. Studies that reported Standardized Mortality Ratios (SMR) for kidney cancer and chronic nephritis/nephrosis in uranium – exposed humans were identified. Studies that reported data for urine protein excretion, glomerular filtration rate, urine albumin, globulin (URM) (BFM) of uranium were included. High uranium exposure and control groups were identified. The Mantel – Haenszel Method was used for all SMR analyses. Inverse Variance with Mean Differences (MD) was used for all biomarker analyses. The diagnosis of renal disease was defined using a median age.

Results: 25 studies were included in the analyses. The mortality studies were exclusively occupational exposures and were divided into a uranium miner/miller subgroup and a factory/nuclear worker subgroup. Exposure subgroups were not created for the biomarker analyses due to an insufficient number of studies. Mortality analyses of kidney cancer and chronic nephritis/nephrosis irrespective of exposure group demonstrated an SMR of 0.93 (95CI: 0.82 – 1.05) and 0.82 (95CI: 0.70 – 0.96), respectively. The subgroup analyses demonstrated similar mortality deficits. The MD analysis of urine BGM (3.41, 95 CI: -5.21 – 12.03) showed higher levels in the high exposure group.

Conclusions: Uranium workers are not at increased risk of death due to renal disease. The current literature is limited to only occupational exposures, thus future community – based studies are needed to fully elucidate the effects of uranium exposure on morbidity and mortality due to renal disease by alleviating the presence of a “healthy worker effect”. In the workers studies, non-cancer related renal disease may be under recognized.
as a contributor to morbidity / mortality. The BMI mg analysis suggests there are possible nephrotoxic effects of uranium exposure, though more studies are needed to improve precision.

**Funding:** Clinical Revenue Support

**PUB312**

Nephrology eConsultation: A Progress Update

David S. Levy, Rickinder Grewal, Monica L. Ranaleta, Stephanie Lempeke, Thu H. Le. University of Rochester Medical Center, Rochester, NY.

**Background:** Given the high demand for nephrology consultation at the University of Rochester, with an average of 30 - 40 new outpatient consultation requests per week, based on the AAMC (Association of American Medical Colleges) Project CORE (Coordinating Optimal Referral Experiences) model, we developed an eConsultation program for primary care providers (PCPs) across the University’s health network to receive subspecialty advice in a prompt and efficient manner in lieu of formal face-to-face nephrology consultation.

**Methods:** Here, we report our experience with time and value-based metrics of our eConsultation program from September 2019 through March 2021. eConsult requests were placed by PCPs for renal-related issues such as mild to moderate acute kidney injury, CKD, electrolyte disturbances, and proteinuria. The nephrologist electronically communicated with the PCP who then conveyed the subspecialty recommendations with their patient.

**Results:** Between September 2019 and March 2021, 338 eConsult requests were received, averaging 17.8 eConsults/month. Of these, 47% were deemed medically appropriate and completed, 34% were converted to in-person visits and 4% were declined. The majority – 63% of eConsults were completed between 11 - 20 minutes, 35% were completed between 5-10 minutes, and only 2% required more than 20 minutes to complete the consult. From a financial perspective, between September 2019 and March 2021, the nephrology eConsult program has generated over $6500 in revenue, translating to ~$38 per encounter, the equivalent of 0.7 wRVUs. From an access standpoint, eConsults were generally completed within 1-2 business days whereas the average wait time for an in-person consultation from referral creation was 33.8 ± 3.7 days.

**Conclusions:** Our nephrology eConsult program has provided timely and remote subspecialty guidance for PCPs within our University’s health network and has overall been well-received by patients and PCPs. This model has the ability to decrease wait time for more complex patients requiring in-person consultation thereby improving the overall quality of care we provide to all of our patients, while still maintaining, if not improving, financial feasibility. Further expansion of the program to involve non-University affiliated PCPs may further improve the program’s ability to provide prompt quality care and better access for patients in more remote areas.

**Funding:** Clinical Revenue Support

**PUB313**

eGFR Trajectory and Risks of Cardiovascular Events and ESKD in CKD Patients

Kohei Ohori, Maiko Kokubu, Masaru Matsui. Nara Prefecture General Medical Center, Nara, Japan.

**Background:** Growing evidence has shown the eGFR level is an established predictor of cardiovascular events, but the association of eGFR trajectory with cardiovascular and renal events remained limited.

**Methods:** We conducted a retrospective cohort study on 276 CKD patients in whom at least two measurements of eGFR levels to calculate eGFR slope were confirmed. Patients were divided into two groups according to the below and above cut-off values of eGFR slopes for outcomes using ROC curve. Outcomes are cardiovascular events defined as heart failure requiring hospitalization, revascularization for IHD and PAD, stroke or sudden death, and renal events defined as ESRD or baseline eGFR decline of >30%.

**Results:** In total, the median (IQR) age of participants was 68 (56-77) years and 176 (64%) were male. The median (IQR) levels of baseline eGFR were 33 (20-48) mL/min/1.73m² and the median eGFR slope of -5.2 (-0.85 to -9.5) mL/min/1.73m²/yr. During the study period, 92 cardiovascular events and 89 renal events occurred. Crude Kaplan-Meier analysis showed patients with lower eGFR slopes had higher probabilities of cardiovascular and renal events with statistical significances (p=0.001 and p=0.001, respectively). In the fully adjusted model, having lower eGFR slopes were associated with HRs (95%CIs) for cardiovascular and renal events of 1.71 [1.08-2.70] and 1.79 [1.09-2.93], respectively.

**Conclusions:** These data suggest not only current eGFR but also eGFR trajectory is an independent risk factor for cardiovascular and renal events in CKD patients.

**PUB314**

Baseline Renal Characteristics and Trial Design for MIRROR RCT, Randomized Trial of Pegloticase with or Without Methotrexate for Uncontrolled Gout

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**Background:** Twenty four percent of patients with gout1 and 49% of patients with uncontrolled gout (UCG)2 patients have CKD. Pegloticase (a pegylated recombinant uricase which rapidly dissolves urate) is associated with a 42% response rate,3 however preliminary evidence suggests co-therapy with immunomodulation such as methotrexate (MTX) may increase this response.4 The ongoing MIRROR randomized controlled trial (RCT) directly compares pegloticase w/MTX for UCG. We describe study design and baseline renal characteristics.

**Methods:** Enrolled patients had a serum urate [SU] ≥ 7 mg/dL, urate lowering therapy failure intolerance, and NO visible tophi, recurrent flares, or chronic gouty arthropathy. Chronic immunosuppression, eGFR-<40 mL/min/1.73m², and G6PD deficiency were key exclusion criteria. Patients who tolerated a 2-wk 15 mg/kg oral MTX run-in were randomized 2:1 to receive MTX or placebo (PBO). After a 4-wk MTX or PBO period, patients began 52 wks of pegloticase with weekly MTX or PBO. Primary endpoint is 6-month response rate (% patients with SU<6 mg/dL for ≥80% during Month 6).

**Results:** 42 US sites randomized 152 adults (54.7±12.6 yrs, 89% women, BMI 32.6±6.5 kg/m²) with UCG (SU 8.9±1.6 mg/dL, 13.9±10.7 yr gout history, 68% with clinical tophi). 21% had prior kidney stones. Mean eGFR was 69.7±17.8 mL/min/1.73m² with 32% having eGFR-<60 mL/min/1.73m². Gout burden became more severe as CKD stage increased, as indicated by Physician Global Assessment, Health Assessment Questionnaire (HAQ), and affected joint count.


**Funding:** Commercial Support - Horizon Therapeutics plc

Mean values of gout severity assessments

**PUB315**

Clinical Outcomes Associated with Systemic Lupus Erythematosus (SLE) Over the 5 Years Prior to ESKD Diagnosis

Christopher F. Bell, Amy Guisinger, Shirley Huang, GlaxoSmithKline, GlaxoSmithKline, 27709, NC.

**Background:** Lupus nephritis affects up to 38% of patients (pts) with SLE, many of whom may progress to ESKD.1 Despite high disease burden, data on clinical characteristics of pts with SLE in the years leading to ESKD diagnosis are limited. This study describes and compares the clinical outcomes of pts with SLE in the 5 years prior to ESKD diagnosis.

**Methods:** This retrospective analysis (GSK, Study 215295) of United States administrative claims data (from IBM MarketScan database) included adult pts with SLE newly diagnosed with ESKD (International Classification of Diseases codes ICD-9/10) from March 2012 to December 2018. Study results focus on clinical outcomes in pts with 5-year continuous enrollment pre ESKD diagnosis.

**Results:** Of 1356 pts with SLE and ESKD identified, 81.8% were female; mean (standard deviation, SD) age was 46.7 (12.3) years. Of these pts, 616 had 5 years of continuous enrollment pre ESKD. Over the 5-year period pre ESKD, mean (SD) Quan-Chen Comorbidity score increased from 1.8 (1.5) in Year 5 to 3.1 (2.0) in Year 1 prior to ESKD. The proportion of pts with severe disease also increased from 31.3% in Year 5 to 51.1% in Year 1 pre ESKD, and more pts experienced SLE flares (80.5% in Year 5 and 94.8% in Year 1 pre ESKD), particularly severe flares (Year 5: 11.9%; Year 1: 13.1%). Renal outcomes worsened each year for the 5-year period (Figure).

**Conclusions:** Prior to ESKD diagnosis, pts with SLE had high disease burden, particularly renal-related, which increased in the years leading to ESKD.

**Funding:** Commercial Support - GlaxoSmithKline
Gout in Advanced CKD Patients: Prevalence and Impact on Patient Health

Leonard Stern,1 Richard J. Johnson,2 Payam Shakouri,1 Amod Athavale,4 Karim R. Masri,1 Brian LaMoreaux,3 Brad Marder,2 Streekalin M. Mandayam,2 Columbia University Irving Medical Center, New York, NY; 1UCHealth University of Colorado Hospital, Aurora, CO; 2Advanced Kidney Care, Poughkeepsie, NY; 3Trinity Life Sciences, Waltham, MA; 4Bon Secours Rheumatology Center, Richmond, VA; 3Horizon Therapeutics plc, Deerfield, IL; 4The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Gout is associated with higher mortality risk,1 multiple comorbidities,2,3 and decreased quality of life.4 Impaired renal function increases gout risk,5 but gout prevalence and impact on advanced CKD patients have not been thoroughly described. This study reports health burden of gout in CKD patients under the care of nephrologists.

Methods: Nephrologists provided chart data on random Stage 3-5 CKD patients. Criteria to identify gout in this study: gout listed as comorbidity, urate-lowering therapy (ULT) use, or visible tophi/gout flare noted. Uncontrolled gout (UCG) was defined as serum urate >6 mg/dL with visible tophi, a2 flares in past year, or a1 swollen/tender joint. Gout prevalence was examined with patients and without gout were compared.

Results: 111 physicians reported on 746 patients (55% male, 56.2±18.3 yrs, BMI: 31.4±10.9 kg/m²) with Stage 3-5 CKD (duration: 4.0±4.8 yrs, eGFR: 32.2±15.5 ml/min/1.73 m²). 173 (23%) met gout criteria, with highest frequency in Stage 3b and 4 (both 28%). Of gout patients, 13% had UCG, 29% had no formal gout diagnosis, and 38% were not using a ULT. Compared to those without gout, patients more often sought acute medical care (30% vs 7% in pri yr) and, at presentation, more often had urination changes (15% vs 7%) and shortness of breath (21% vs 14%; all p<0.02). Gout patients had more diagnoses of CKD-mineral bone disorder, ischemic heart disease, CHF, peripheral vascular disease, and chronic pain. Compared to controlled gout patients, UCG patients more often had pulmonary hypertension, joint issues, chronic pain, febuxostat use, and uricosuric use.


Funding: Commercial Support - Horizon Therapeutics plc

Claims-Based Evaluation of Pegloticase Use in Gout Patients with a History of Kidney Transplant

Craige Alan Shadur,1 Karim R. Masri,1 Brad Marder,2 Claudia C. Vesel,3 Brian LaMoreaux,1 Kidney Physicians, PC, Des Moines, IA; 2Bon Secours Mercy Rheumatology Center; Richmond, VA; 3Horizon Therapeutics plc, Deerfield, IL.

Background: Kidney transplant (KT) recipients have a high incidence of gout due to reduced GFR and medications associated with hyperuricemia. Impaired renal function and drug interaction concerns can make it challenging to effectively lower urate in this population. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and has known efficacy for managing uncontrolled gout. However, clinical trials excluded organ transplant recipients and few cases of use in transplant recipients have been reported. This study examined pegloticase use in KT patients with uncontrolled gout in a large claims database.

Methods: The IQVIA database was used to identify pts with a history of KT (as CPT or ICD O080 code) receiving a1 pegloticase infusion. The number and type of concurrent immunosuppression (IMS) prescriptions within 3 mo prior to/during pegloticase use were collected and the number of pegloticase infusions was evaluated. Pts were excluded if they returned to dialysis before the first pegloticase infusion because of graft failure or rejection.

Results: 91 pts were identified between 2015 and 2020. Pts with reported demographics (n=85) were predominately male (81%) and 58±11 yrs old at the time of first pegloticase infusion. The most common comorbidities were hypertension (84%), hyperlipidemia (48%), anemia (46%), type 2 diabetes mellitus (40%), and heart failure (34%). Compared to 1st pegloticase claim, the 1st transplant code was 2.6±1.7 yrs (mean ± SD) earlier and 1st gout code was 2.1±1.7 yrs earlier. 61 pts (67%) had a tophaceous gout code. Transplant IMS medication codes were available for 67 pts (74%), with the majority receiving tacrolimus (n=34), mycophenolate mofetil (n=33), and or cyclosporine (n=29). Pts received a mean of 13±16 pegloticase infusions (median: 8; Q1: Q3: 4, 15), with 38% receiving ≥12 infusions and 20% receiving ≥20 infusions.

Conclusions: This real-world dataset demonstrated that KT patients with uncontrolled gout are being treated with pegloticase. A main consideration with pegloticase efficacy is potential development of anti-drug antibodies (ADAs). Given that solid-organ transplant patients are on IMS medications to preserve their grafted organ, this likely contributed to prevention of ADAs indicated by the longer average duration of therapy compared to other real-world pegloticase datasets.

Funding: Commercial Support - Horizon Therapeutics plc

Safety of Pegloticase with Immunomodulation Co-Therapy: Literature Review

Jeff R. Peterson,1 Nathan Roe,2 Howard M. Kenney,1 Abdul A. Abdellatif,4 Brian LaMoreaux,3 Western Washington Medical Group Arthritis Clinic, Bothell, WA; 2Horizon Therapeutics plc, Deerfield, IL; 3Arthritis Northwest, Spokane, WA; 4Baylor College of Medicine, Division of Nephrology, Houston, TX.

Background: Gout occurs frequently among Chronic Kidney Disease (CKD) patients. Pegloticase therapy for uncontrolled gout does not require renal adjustments and is effective across all stages of CKD. Efficacy can be limited by development of anti-drug antibodies, which also increase the risk of infusion reactions (IR). A recent study reviewed publications on pegloticase with immunomodulating (IMM) co-therapy and demonstrated an increased response rate compared to the pivotal trials; however, aggregate safety data from the literature has not been reported.1 The purpose of this study is to report IR prevalence and adverse events (AEs) of interest in publications which have evaluated the co-prescription of IMM with pegloticase.

Methods: Studies of pegloticase (≥2w) use with concurrent IMM were identified in a search of PubMed and abstracts from professional society meetings (2012-2020). Articles were extracted and reported including IRs, gout flares, and infections. Gout flares and infection occurrence were not described in all studies, therefore, only studies where occurrence was specifically addressed were included.

Results: 10 publications were identified using IMM with pegloticase consisting of 82 total patients. Methotrexate was the most common IMM co-therapy. Due to the frequency of CKD in gout patients, other IMM agents were frequently used, including mycophenolate mofetil, leflunomide, azathioprine, and cyclosporine. All reports included serum urate monitoring to evaluate the ongoing efficacy of pegloticase. 3/82 (4%) patients experienced an IR during pegloticase therapy (total of 3 IRs) (IR C). A recent review studied reported publications on pegloticase with immunomodulating (IMM) co-therapy and demonstrated an increased response rate compared to the pivotal trials; however, aggregate safety data from the literature has not been reported.1 The purpose of this study is to report IR prevalence and adverse events (AEs) of interest in publications which have evaluated the co-prescription of IMM with pegloticase.

Conclusions: Pegloticase administered with IMM co-therapy had a low rate of mild IRs with no anaphylaxis reported. This study demonstrates that in addition to established improvements in pegloticase efficacy, the use of IMM co-therapy with pegloticase results in a favorable response rate and safety profile with low rate and severity of infections. Gout flares and infection occurrence were not described in all studies, therefore, only studies where occurrence was specifically addressed were included.

Funding: Commercial Support - Horizon Therapeutics plc

Prediction of Mortality Among Patients with CKD: A Systematic Review

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Background: Chronic kidney disease (CKD) is a common medical condition with an increasing prevalence. To date, several clinical characteristics have been shown to be associated with mortality in CKD patients from regression analyses. However, the accuracy of mortality prediction has not been clearly elucidated. Thus, we aimed to demonstrate the predicting factors for mortality among CKD patients by utilizing the area under the receiver operating characteristic curve (AUC) analysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched through January 2021. Inclusion criteria were: 1) observational studies; 2) populations were non-transplant CKD at any stage; and 3) results were presented with AUC analysis with 95% confidence interval. AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

Results: A total of 18 studies (n = 14,579) were included in the systematic review. 832 confirmed deaths were identified. The area under the curve (AUC) for the prediction of mortality among CKD patients of eGFR ≥60 was 0.71 (95% CI 0.69-0.73, p<0.001). Among the 36 published variables, among the 36 published variables, some of which were echocardiographic factors (Image 1). 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction.

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

PUB320

Utilization of Renin Angiotensin Aldosterone System Inhibitors in Cardiorenal Syndrome Patients: An Experience from the Middle East

Amir Yosef Cardiorenal Syndrome Patients: An Experience from the Middle East

J Am Soc Nephrol 32: 2021

Practical tool for mortality prediction in this population. A total of 18 studies (n = 14,579) were included in the systematic review. 832 confirmed deaths were identified. The area under the curve (AUC) for the prediction of mortality among CKD patients of eGFR ≥60 was 0.71 (95% CI 0.69-0.73, p<0.001). Among the 36 published variables, some of which were echocardiographic factors (Image 1). 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction.

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

PUB321

Renal Function Outcomes at 5 Years from Radical and Partial Nephrectomies in Normal Renal Function Patients: An Intriguing Tale of Failed Renal Hypermorphers

Francesco Trevisani,1 Federico Di Marco,1 Matteo Fioris,2 Francesco Trepecione,3 Giuseppe Rosiello,1 Antonello Pani,1 Giovambattista Capasso,1 Caterina Vitaligiano,1,2 Giacomo Mischitz,3 Francesco Fiorio,1 Alessandra Cinque,1 Arianna Bettiga,1 Alessandro Larcher,1 Umberto Capitanio,1 Andrea Salonia,1 Francesco Montorsi.1 IRCCS Ospedale San Raffaele, Milano, Italy; 2Ospedale Giuseppe Brotzu, Cagliari, Italy; 3Università degli Studi della Campania Luigi Vanvitelli Dipartimento di Scienze Mediche Translazionali, Napoli, Italy; 4Biogem, Institute of biology and genetics, Avezzano, Italy.

Background: CKD represents a major postoperative long-term complication in renal surgery, both in radical (RN) than in partial nephrectomy (PN). Aim of our study was to compare the eGFR decay over time from pre-operative time surgery to 5 years follow up in RN and PN in normal renal function pts.

Methods: A multicentric cohort-study of 269 consecutive pts who underwent RN or PN due to the presence of a kidney mass was enrolled. A group of 42 kidney living donors was considered as control. We evaluated eGFR variation at the pre-surgical visit, hospital dismissal, 6,12,24,36,48,60 months. eGFR categories were created according to K-DIGO system. Comparisons between groups were performed using Kruskal-Wallis ranks sum test for numerical variables and Pearson’s Chi square test for categorical variables.

Results: A total of 18 studies (n = 14,579) were included in the systematic review. 832 confirmed deaths were identified. The area under the curve (AUC) for the prediction of mortality among CKD patients of eGFR ≥60 was 0.71 (95% CI 0.69-0.73, p<0.001). Among the 36 published variables, some of which were echocardiographic factors (Image 1). 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction.

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

Conclusions: Renal and PN harbor a solid risk of post-operative CKD even in normal renal function pts. RN pts tend to vicariate the acute loss of nephron mass with an increase of eGFR over time, while PN renal function remains stable in time without hyperfiltration.

Table 1: Characteristics of IF patients with CRS vs. those without CRS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRS IF patients</th>
<th>Non-CRS IF patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.5 ± 12.2</td>
<td>74.8 ± 12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>78%</td>
<td>62%</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.0%</td>
<td>9.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87%</td>
<td>64.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7.5%</td>
<td>9.5%</td>
<td>0.02</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>22.5%</td>
<td>17.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-Solomon</td>
<td>33.5%</td>
<td>25.5%</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>27.5%</td>
<td>33.5%</td>
<td>0.9</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>15.5%</td>
<td>18.5%</td>
<td>0.7</td>
</tr>
<tr>
<td>Systolic pulmonary artery</td>
<td>16.5%</td>
<td>18.5%</td>
<td>0.7</td>
</tr>
<tr>
<td>Echocardiographic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial reservoir strain</td>
<td>7th</td>
<td>97.5%</td>
<td></td>
</tr>
<tr>
<td>Right atrial reservoir strain</td>
<td>7th</td>
<td>97.5%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery pressure</td>
<td>16.5%</td>
<td>18.5%</td>
<td>0.7</td>
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<tr>
<td>Echocardiographic factors</td>
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<tr>
<td>Left atrial reservoir strain</td>
<td>7th</td>
<td>97.5%</td>
<td></td>
</tr>
<tr>
<td>Right atrial reservoir strain</td>
<td>7th</td>
<td>97.5%</td>
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<tr>
<td>Pulmonary artery pressure</td>
<td>16.5%</td>
<td>18.5%</td>
<td>0.7</td>
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<tr>
<td>C-reactive protein</td>
<td>15.5%</td>
<td>18.5%</td>
<td>0.7</td>
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<tr>
<td>Systolic pulmonary artery</td>
<td>16.5%</td>
<td>18.5%</td>
<td>0.7</td>
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Background: CKD represents a major postoperative long-term complication in renal surgery, both in radical (RN) than in partial nephrectomy (PN). Aim of our study was to compare the eGFR decay over time from pre-operative time surgery to 5 years follow up in RN and PN in normal renal function pts.

Methods: A multicentric cohort-study of 269 consecutive pts who underwent RN or PN due to the presence of a kidney mass was enrolled. A group of 42 kidney living donors was considered as control. We evaluated eGFR variation at the pre-surgical visit, hospital dismissal, 6,12,24,36,48,60 months. eGFR categories were created according to K-DIGO system. Comparisons between groups were performed using Kruskal-Wallis ranks sum test for numerical variables and Pearson’s Chi square test for categorical variables.

Results: A total of 18 studies (n = 14,579) were included in the systematic review. 832 confirmed deaths were identified. The area under the curve (AUC) for the prediction of mortality among CKD patients of eGFR ≥60 was 0.71 (95% CI 0.69-0.73, p<0.001). Among the 36 published variables, some of which were echocardiographic factors (Image 1). 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction.

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

Conclusions: Renal and PN harbor a solid risk of post-operative CKD even in normal renal function pts. RN pts tend to vicariate the acute loss of nephron mass with an increase of eGFR over time, while PN renal function remains stable in time without hyperfiltration.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Outcomes of Educational Initiatives for Advanced CKD


Background: Timing of kidney replacement therapy (KRT) and transplant referral in chronic kidney disease (CKD) G4 and G5 is a difficult topic. The COVID-19 pandemic has disrupted nearly all aspects of healthcare, including the process of KRT plan. This study examined if the addition of a Transition Coordinator (TC) improved KRT plan transition despite the pandemic.

Methods: Retrospective descriptive study examining patients at single academic practice with eGFR <20 that completed CKD educational program (CKDEP). Control Group: 5/1/19-1/31/20 with virtual or in-person CKDEP, no TC. Intervention Group (IG): 5/1/20-1/31/21 with virtual or in-person CKDEP with addition of TC. TC called patient monthly to assess barriers to KRT planning, assist with scheduling, and communicate with Nephrologist. “Success” was defined as having a KRT plan. Failure was defined as either urgent start dialysis via dialysis catheter (DC) or patients without KRT plan.

Results: CG had n=15 while IG had n=47. Both groups were evenly distributed with age, average eGFR (15). The CG had slightly higher rates of urgent starts and patients without KRT plan compared to IG (Table 1). Patients were referred for Vascular access +/- Transplant 20% (3) in CG and 23% in IG. PD +/- Transplant was chosen in 6.7% (1) of CG and 36% (17) of IG. Success and Failure rates were similar in both groups (Table 2).

Conclusions: Despite the pandemic, there was no overall change in rate of failure (urgent start or lack of KRT plan), however, individual decreases in these groups were noted. This could indicate that TC may improve outcomes when the pandemic is controlled. Increased interest in PD was noted which could indicate greater understanding via follow-up provided by TC.

<table>
<thead>
<tr>
<th>Table 1. Percentage of Urgent KRT vs no KRT plan due to intervention</th>
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<tr>
<td>Urgent start KRT</td>
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<tr>
<td>No KRT plan</td>
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<td>Total</td>
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Table 2

<table>
<thead>
<tr>
<th>Table 2. Control Group Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Success</td>
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<td>Total</td>
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</table>

100.0% |

PUB324

Inhibition of Old Astrocyte Specifically Induced Substance (OASIS) in Myofibroblasts Suppressed Kidney Fibrosis

Ayaha Yamamoto,1 Masanori Obana,1 Yoshiaki Miyake,1 Shota Tanaka,1 Makiko Maeda,1 Kazunori Imazumi,2 Yasushi Fujio,1 Osaka Daigaku, Suita, Japan; 2Hiroshima Daigaku, Higashihiroshima, Japan.

Background: Although kidney fibrosis is a critical event for the onset of renal failure, molecular mechanisms are not fully understood. Previously, we found that Old astrocyte specifically induced substance (OASIS), a transcription factor, exacerbated kidney fibrosis in part by increased bone marrow stromal cell antigen 2 (B2u), using conventional knockout mice; however, the cell specificity of OASIS function in kidney fibrosis remains to be elucidated. In this study, we focused on the role of OASIS in myofibroblasts to elucidate novel mechanisms of kidney fibrosis.

Methods: OASIS expression in human kidneys was examined by immunohistochemistry with anti-OASIS and α-SMA antibodies. Cultured myofibroblasts were treated with AEBSF, an inhibitor of OASIS activation. In addition, C57BL/6 mice were intraperitoneally injected with AEBSF for 9 consecutive days starting 2 days before unilateral ureteral obstruction (UUO) surgery. To examine the effects of OASIS in myofibroblasts on kidney fibrosis, myofibroblast-specific OASIS knockout (cKO) mice were subjected to UUO. Day 7 after UUO, kidney fibrosis was examined by Sirius Red staining, hydroxyproline assay and immunofluorescence analysis. Isolated murine myofibroblasts were treated with TGF-β1 for 24 hours and chromatin immunoprecipitation assay was conducted to test whether OASIS directly regulates the transcription of Collagen I and Bst2.

Results: OASIS was increased in fibrotic kidneys in human fibrotic kidneys. AEBSF suppressed OASIS activation in myofibroblasts and reduced kidney fibrosis after UUO. Importantly, kidney fibrosis was attenuated in OASIS cKO mice compared with control mice (Sirius Red positive area (%); Control-contralateral;5.2±2.9, cKO-contralateral;3.1±1.0, cKO-UUO;18.8±2.0, n=6-9). In addition, OASIS cKO mice showed reduced number of Ki-67-positive proliferative myofibroblasts in fibrotic kidneys. Finally, mRNA levels of Collagen I and Bst2 was decreased in the kidneys of OASIS cKO mice after UUO and OASIS directly bound to the promoter region of these genes in murine kidney myofibroblasts.

Conclusions: OASIS in myofibroblasts contributes to the development of kidney fibrosis. Suppression of OASIS signaling in myofibroblasts could be a novel therapeutic strategy against fibrotic kidney disease.

PUB325

Salvianolic Acid C Activates PPAR Signaling Pathway and Ameliorates Renal Fibrosis in Obstructive Kidneys

Junyan Lin, Ming Wu, Dongping Chen, Chaoyang Ye. Shuguang Hospital, Shanghai, China.

Background: Salvianolic acid C (SAC) is a component of Danshen, a widely used herbal medicine for the treatment of renal cardiovascular diseases. Renal interstitial fibrosis is a common pathway of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. We aimed to study the effect of SAC on renal fibrosis and explore its underlying mechanisms.

Results: Warfarin treatment resulted in a PT increase 1.5-2.5 times from control, increase in hematuria and serum creatinine. Histologically, warfarin-treated animals had more iron-positive tubular epithelial cells and increased IFTA as compared to control (42.9±7% vs 18.3±2.6%). Fig 1. ROS were increased in the kidney in warfarin-treated rats. The number of tubules that show evidence of EMT was significantly higher in warfarin-treated 5/6NE as compared to control 5/6NE rats.

Conclusions: Chronic hematuria results in increased iron-positive tubular epithelial cells, EMT and more prominent IFTA in CKD rats. Our data suggests an important role of chronic hematuria in the progression of CKD.

Funding: NIDDK Support
Methods: After sham or unilateral ureteral obstruction (UUO) operation, 20-25g male C57BL/6J mice were used with vehicle or SAC (10mg/kg) for 14 days. Moreover, normal rat kidney interstitial fibroblast (NRK-49F) cells were treated with various concentrations of SAC (10 nM to 100 nM). Protein samples from in vivo and in vitro experiments were collected to assess renal fibrosis.

Results: Treatment with SAC reduced the deposition of interstitial matrix proteins in UUO kidneys as shown by Masson staining. The expression of Fibronectin, collagen-I and α smooth muscle actin (αSMA) were increased in UUO induced fibrotic kidneys, which were down-regulated in SAC treated UUO kidneys. In parallel, treatment with SAC increased the expression of fibronectin and collagen-I in NRK-49F cells. RNA-sequence analysis showed that multiple genes belong to the PPAR (peroxisome proliferator-activated receptor) signaling pathway were up-regulated by SAC treatment in UUO kidneys.

Conclusions: SAC inhibits renal fibrosis in obstructed kidneys possibly through activation of the PPAR signaling pathway.

Funding: Government Support - Non-U.S.

PUB326
Role of PAR-1 in Immune Activation and Tubulointerstitial Fibrosis During AKI-to-CKD transition
Sarah W.Y. Lok, Wai Han Yiu, Loretta Y.Y. Chan, Joseph C K Leung, Sydney C. Tang. University of Hong Kong, Hong Kong, Hong Kong.

Background: The high-affinity thrombin receptor protease-activated receptor-1 (PAR-1) has been recognized as a therapeutic target for cardiovascular intervention. Emerging evidence suggests that the coagulation cascade is activated in the kidney interstitium during AKI. Yet, the role of PAR-1 signaling in AKI to CKD transition remains largely unexplored.

Methods: We investigated the effect of PAR-1 deficiency in a longitudinal kidney fibrotic murine AKI to CKD transition model. PAR-1−/− and wild type mice underwent unilateral ischemia-reperfusion injury (UIRI) for 7, 14 and 28 days. Uninephrectomy of the contralateral kidney was performed one day before sacrifice to assess renal injury.

Results: After 14 or 28 days of UIRI, BUN was significantly lower in PAR-1−/− vs wild type mice. PAR-1−/− mice showed diminished kidney fibrosis with reduced ECM accumulation and expression of fibronectin, α smooth muscle actin and collagen via TGF-β/Smad signaling after UIRI. Macrophage infiltration and inflammation was alleviated in PAR-1−/− ischemic kidneys in which macrophage M1-polarization and its secretory cytokine TNF-α were attenuated.

Conclusions: PAR-1 deficiency confers renoprotection by suppressing M1 macrophage activation, inflammatory and profibrotic responses during AKI and its subsequent transition to CKD. Funding: Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (General Research Fund, grant no. 17118720), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 18.

PUB327
Increased Serum ApoCIII Levels in CKD Patients May Underlie the Impaired Delivery of Cholesterol to Hepatocytes and Increased Cardiovascular Disease (CVD) Risk
Graham T. Gibson, Siddhartha S. Ghosh, Todd W. Geehr, Sarah Bu, Jing Wang, Shobha Ghosh, Youngrok Shin, Virginia Commonwealth University, Richmond, VA; VA Richmond Medical Center, Richmond, VA.

Background: Increased CVD risk underlies the mortality in CKD patients but the underlying mechanisms are not completely defined. We reported earlier that the serum from CKD patients displayed an impaired ability to deliver cholesterol to hepatocytes demonstrating a likely defect in hepatic elimination of cholesterol (as bile acids and biliary cholesterol) returning to the liver from the peripheral tissues via lipoproteins (e.g., VLDL or HDL). Apolipoprotein C-III (ApoCIII) is associated with VLDL and HDL and, not only inhibits lipoprotein lipase and hepatic lipase, but inhibits the uptake of VLDL and HDL by hepatic lipoprotein receptors. Herein we examined the hypothesis that impaired ability of serum from CKD subjects to deliver cholesterol to hepatocytes was associated with increased serum ApoCIII.

Methods: ApoCIII levels were determined by ELISA in serum samples from 32 patients with CKD [stage 3 (N=15) and stage 4/5 (N=17)], 15 patients with established CAD and 15 healthy subjects from our earlier study. One-way ANOVA with Multiple group comparisons was used to determine significance of observed differences.

Results: While ApoCIII levels in healthy subjects and patients with established CAD were not significantly different, significantly higher ApoCIII levels were seen in patients with CKD 3 and CKD 4/5 (See Figure) compared to healthy subjects as well as compared to patients with CAD. This is consistent with the reported decrease in hepatocyte uptake of lipoprotein cholesterol from serum of CKD patients.

Conclusions: Circulating ApoCIII, the catabolism of which is related to kidney function, is increased in CKD and likely impairs the ability of VLDL and HDL uptake by hepatocytes. Using ApoCIII transgenic mice, the mechanistic details are currently under investigation.
cytokines

corticosteroids

creatinine

cystic kidney disease

cytokines

cytomegalovirus

cytoskeleton

daily hemodialysis

delayed graft function

dentin dysplasia

dementia

dent disease

depression

diabetes

diabetes mellitus

diabetic glomerulopathy

diabetic glomerulosclerosis

diabetic nephropathy

diabetes related amyloidosis

diabetes volume

diabetes withholding

distal tubule

diuretics

drug excretion

drug interactions

drug metabolism

drug nephrotoxicity

echocardiography

economic analysis

economic impact

economic analysis

elektrolyte disorder

economic analysis
endothelium

eosinophilia
eosinophilia

epidemiology and outcomes

expression

extracellular matrix

failure

family history

fibroblast

fibroconnectin

fibrosis

ESRD (end-stage renal disease)

ESRD (end-stage renal disease) (continued)

gastrointestinal medications

gender difference

gene expression

gene therapy

gene transcription

genetic renal disease

gender difference

gene transcription

endothelium

eosinophilia

epithelial sodium transport

endothelial cells

endothelial sodium channel

epithelial sodium transport

epithelial growth factor

epithelial

epithelial sodium channel

epithelial sodium transport

epitheliopeptin

erythropoietin

esRD (end-stage renal disease)

J Am Soc Nephrol 32: 2021

glomerular disease (continued)............. PO1446,
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PO1902, PO1915, PO1935, PO2215,
PO2232, PO2238, PUB003, PUB172,
PUB196, PUB198, PUB199, PUB226,
PUB240, PUB241, PUB261
glomerular endothelial cells............... TH-OR52,
FR-OR15, FR-OR40, PO0510,
PO0626, PO0645, PO0660, PO0664,
PO1705, PUB244
glomerular epithelial cells..................... PO1398,
PO1671, PO1715
glomerular filtration barrier...............FR-OR33,
PO0434, PO0620, PO1399, PO1657,
PO1670, PO1701, PO1702, PO1705
glomerular filtration rate................... TH-OR61,
TH-OR62, TH-OR64, TH-OR65, TH-OR66,
TH-OR67, FR-OR42, FR-OR51, FR-OR54,
FR-OR58, SA-OR24, PO0168, PO0255,
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PO2285, PO2289, PO2313, PO2317,
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PO2344, PO2347, PO2358, PO2362,
PO2368, PO2388, PO2389, PO2390,
PO2412, PO2419, PO2430, PO2431,
PO2508, PO2518, PUB264
glomerular hyperfiltration.....................PUB304
glomerulonephritis............. FR-OR37, FR-OR49,
SA-OR33, SA-OR50, PO0101, PO0106,
PO0109, PO0284, PO0289, PO0306,
PO1159, PO1407, PO1415, PO1417,
PO1420, PO1423, PO1424, PO1438,
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PO2261, PO2292, PO2446, PO2473,
PUB156, PUB187, PUB189, PUB190,
PUB192, PUB195, PUB199, PUB200,
PUB201, PUB205, PUB206, PUB209,
PUB213, PUB215, PUB217, PUB223
glomerulopathy........ PO0733, PO1397, PO1408,
PO1469, PO1482, PO1485, PO1508,
PO1519, PO1547, PO1574, PO1576,

glomerulopathy (continued).................. PO1600,
PO1632, PO1673, PO1678, PO1699,
PO1716, PO1719, PO1722, PO1892,
PO1894, PO1900, PO1936, PUB220,
PUB222, PUB234
glomerulosclerosis ...............................FR-OR35,
PO0108, PO0218, PO0654, PO1299,
PO1302, PO1315, PO1321, PO1333,
PO1336, PO1399, PO1402, PO1412,
PO1413, PO1458, PO1529, PO1559,
PO1600, PO1637, PO1641, PO1643,
PO1664, PO1672, PO1682, PO1691,
PO1695, PO1697, PO1971, PO1980,
PO2212, PO2513, PUB186
glomerulus..............FR-OR39, PO0493, PO0614,
PO0617, PO0645, PO0677, PO1661,
PO1689, PO1723, PO1724, PO1933
glycation................................................... PO1273
Goodpasture syndrome............PO1622, PUB208
health status.............. PO0824, PO0828, PO0842,
PO0952, PO1296, PO1731, PO1748,
PO1749, PO1756, PO2061, PO2064,
PO2152, PO2276, PO2329, PO2399,
PO2405, PUB253, PUB306
heart disease..............PO0789, PO1051, PUB233
heart failure..... TH-OR14, TH-OR41, TH-OR42,
TH-OR44, FR-OR47, PO0175, PO0300,
PO0387, PO0539, PO0861, PO0874,
PO0945, PO1016, PO1108, PO1111, PO1112,
PO1800, PO1802, PO1803, PO1804,
PO1805, PO1808, PO1826, PO1836,
PO1837, PO1843, PO2120, PO2247,
PO2310, PO2417
heme oxygenase...... SA-OR03, PO0241, PO0363
hemodialysis..... FR-OR25, FR-OR26, FR-OR28,
SA-OR05, PO0014, PO0033, PO0054,
PO0065, PO0066, PO0075, PO0085,
PO0087, PO0091, PO0097, PO0127,
PO0135, PO0136, PO0139, PO0140,
PO0141, PO0142, PO0145, PO0151,
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PO0255, PO0322, PO0468, PO0470,
PO0471, PO0475, PO0487, PO0489,
PO0502, PO0514, PO0538, PO0540,
PO0541, PO0542, PO0549, PO0551,
PO0552, PO0565, PO0587, PO0588,
PO0589, PO0629, PO0772, PO0773,
PO0796, PO0798, PO0800, PO0804,
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PO0817, PO0818, PO0821, PO0822,
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PO0833, PO0834, PO0843, PO0845,
PO0848, PO0850, PO0852, PO0853,
PO0856, PO0859, PO0863, PO0864,
PO0865, PO0867, PO0869, PO0870,
PO0871, PO0874, PO0877, PO0878,
PO0879, PO0881, PO0882, PO0887,
PO0888, PO0889, PO0893, PO0894,
PO0895, PO0896, PO0903, PO0908,
PO0910, PO0911, PO0913, PO0914,
PO0915, PO0916, PO0917, PO0919,
PO0921, PO0922, PO0923, PO0926,
PO0927, PO0928, PO0929, PO0931,
PO0932, PO0935, PO0936, PO0938,
PO0939, PO0943, PO0944, PO0954,
PO0955, PO0970, PO0975, PO0994,
PO1023, PO1033, PO1036, PO1043,
PO1046, PO1052, PO1106, PO1167,
PO1170, PO1175, PO1373, PO1374,

899

hemodialysis (continued)........ PO1375, PO1376,
PO1549, PO1734, PO1748, PO1799,
PO1800, PO1964, PO1966, PO1967,
PO2138, PO2274, PUB010, PUB015,
PUB017, PUB018, PUB019, PUB022,
PUB030, PUB031, PUB032, PUB033,
PUB041, PUB061, PUB071, PUB076,
PUB089, PUB092, PUB096, PUB098,
PUB101, PUB102, PUB104, PUB105,
PUB110, PUB115, PUB118, PUB120,
PUB132, PUB136, PUB153, PUB242
hemodialysis access................. PO0886, PO1019,
PO1022, PO1035, PO1036, PO1037,
PO1039, PO1040, PO1045, PO1047,
PO1048, PO1054, PUB006, PUB136
hemodialysis adequacy.......................... PO0931,
PO0934, PUB096
hemodialysis hazards.............. PO0290, PO0876,
PO0895, PO0904, PO1047,
PO1968, PUB034, PUB111
hemolytic uremic syndrome.................. PO0125,
PO0239, PO0293, PO0296, PO0311,
PO1364, PO1465, PO1505, PO1551,
PO1655, PO1717, PO1985, PO2013,
PO2229, PO2230, PO2237, PUB221
hemoperfusion.........FR-OR28, PO0161, PO1053
Henoch-Schonlein purpura..... PO1513, PO1521
hepatitis...................FR-OR55, PO0810, PO0811,
PO1580, PO1605, PUB103, PUB292
histopathology....... TH-OR51, PO0197, PO0374,
PO0906, PO1224, PO1397, PO1584,
PO1867, PUB045, PUB201
HIV nephropathy................. TH-OR03, PO1333,
PO1520, PO1526, PO1665,
PO1666, PO1697, PO2111
hospitalization....... TH-OR06, PO0026, PO0054,
PO0058, PO0059, PO0119, PO0175,
PO0203, PO0236, PO0242, PO0814,
PO0841, PO0907, PO0912, PO0957,
PO0969, PO0982, PO1124, PO1142,
PO1156, PO1272, PO1373, PO1758,
PO1969, PO2311, PO2351, PO2353,
PO2402, PUB025, PUB088
human genetics.......FR-OR41, PO0810, PO1062,
PO1347, PO1687, PO2053, PO2176
hyaluronidase.......................................... PO2512
hypercalciuria........................... PO0572, PO1203
hypercholesterolemia..............................PUB067
hyperfiltration........... PO1695, PO2244, PO2498
hyperglycemia.......... PO0693, PO0694, PO0783,
PO1150, PO1742
hyperkalemia............ PO0257, PO0537, PO0892,
PO1127, PO1129, PO1134, PO1920,
PO2369, PO2370
hypernatremia.......... PO0074, PO0076, PO0169,
PO0257, PO0515, PO1143, PO1153,
PO1156, PO1158, PUB152
hyperparathyroidism........ TH-OR11, TH-OR18,
TH-OR19, PO0516, PO0521, PO0547,
PO0549, PO0551, PO0553, PO0563,
PO0575, PO0589, PO1385, PUB074,
PUB075, PUB076, PUB079, PUB082
hyperphosphatemia.......... TH-OR16, TH-OR18,
PO0532, PO0537, PO0540, PO0541,
PO0542, PO0545, PO0567, PO0593,
PO0799, PO0998, PO1195, PO1285,
PO1732, PO1733, PO2501


potassium (K) channels……. PO1061, PO1091, PO1093, PO1122, PO1127, PO1130, PO1131, PO2258, PUB143, PUB144
primary glomerulonephritis………… PO1545, PO1642
progression………… SA-OR39, PO0210, PO0399, PO6082, PO1649, PO2302, PO2346, PO2350, PO2386, PS, PO2406, PO2455, PO2456, PO2518, PUB58
progression of renal failure…………...... TH-OR63, TH-OR68, FR-OR51, SA-OR12, SA-OR25, SA-OR43, PO0235, PO4417, PO7041, PO7054, PO8085, PO8106, PO8129, PO1556, PO1569, PO1582, PO1592, PO1597, PO1599, PO1788, PO1813, PO1895, PO1972, PO1973, PO2044, PO2144, PO2337
proliferation……………… SA-OR14, PO0414, PO0420, PO0431
proteinuria……… TH-OR28, PO0040, PO107, PO1010, PO1112, PO1116, PO2218, PO3004, PO6070, PO1000, PO1095, PO1326, PO1335, PO1410, PO1493, PO1509, PO1513, PO1524, PO1529, PO1530, PO1534, PO1540, PO1561, PO1569, PO1570, PO1572, PO1576, PO1577, PO1578, PO1595, PO1597, PO1624, PO1631, PO1639, PO1641, PO1643, PO1644, PO1648, PO1653, PO1657, PO1658, PO1674, PO1676, PO1700, PO1710, PO1711, PO1735, PO1882, PO1907, PO1922, PO1948, PO2037, PO2126, PO2131, PO2221, PO2554, PO2263, PO2355, PO2369, PO2438, PUB003, PUB041, PUB179, PUB181, PUB188, PUB207, PUB261, PUB232
proximal tubule……………… TH-OR15, FR-OR50, SA-OR16, SA-OR59, PO0004, PO0009, PO0011, PO0181, PO0335, PO0337, PO0388, PO0411, PO0412, PO0433, PO0438, PO0445, PO0449, PO0495, PO0515, PO0584, PO0641, PO0668, PO0697, PO0714, PO0729, PO1263, PO1352, PO1432, PO1831, PO1879, PO1907, PO1921, PO2017, PO2425, PO2494, PO2500, PO2521, PO2605
pyelonephritis………… PO0285, PO1100, PO1984, PO1986, PO1987, PO2005
quality of life……………… FR-OR53, FR-OR60, PO0090, PO0097, PO0185, PO0565, PO8111, PO0813, PO0827, PO831, PO833, PO843, PO842, PO847, PO848, PO858, PO862, PO9091, PO9049, PO9076, PO1002, PO1257, PO1376, PO1378, PO1379, PO1380, PO1479, PO1755, PO1804, PO1864, PO2006, PO2008, PO2057, PO2063, PO2065, PO2084, PO2140, PO2141, PO2277, PO2287, PO2346, PO2407, PO2418, PUB262
RAGE (receptor for AGES)………… PO1822
randomized controlled trials………… SA-OR32, PO0457, PO0460, PO0461, PO0462, PO0463, PO0464, PO0482, PO0784, PO0805, PO0818, PO1224, PO1634, PO1652, PO1807, PO1812, PO2396, PO2412
reactive oxygen species…… FR-OR43, PO0526, PO0713, PO0715, PO1663
regulation………… PO0087, PO0429, PO1094, PO1429, PO2479
rejection……………… TH-OR51, TH-OR54, PO2108, PO2173, PO2175, PO2176, PO2180, PO2194, PO2195, PUB28
renal ablation……………… PO1704, PO1811, PO1817
renal artery stenosis……………… TH-OR44, PO0328, PO0634, PO1807, PO1808, PO1809, PO1833, PO1668, PUB238
renal biopsy……………… FR-OR48, PO1011, PO1026, PO2281, PO2285, PO2293, PO3013, PO3017, PO3022, PO1475, PO1494, PO1531, PO1547, PO1575, PO1576, PO1601, PO1602, PO1628, PO1846, PO1922, PO1926, PO1931, PO1933, PO2130, PO2195, PO2190, PUB53, PUB208, PUB220, PUB246, PUB254, PUB261, PUB266
renal carcinoma……………… PO1501, PO1621, PO1595, PO1853, PO1855, PO1859, PUB242
renal cell biology……………… TH-OR39, FR-OR38, SA-OR24, PO0340, PO0507, PO0616, PO0619, PO7031, PO1121, PO1232, PO1236, PO1248, PO1265, PO1456, PO2492, PUB195
renal development……………… SA-OR48, PO0240, PO6057, PO6068, PO6693, PO1310, PO2476
renal diastasis……………… FR-OR21, PO1599, PO2909, PO9941, PO2033, PUB124
renal dysfunctions……………… PO0007, PO0224, PO2099, PO1131, PO1353, PO1805, PO1812, PO1818, PO1819, PO2519
renal epithelial cell……………… PO608, PO6019, PO709, PO1103
renal failure……………… PO0165, PO7999, PO964, PO1915, PO3139, PO1589, PO1607, PO1985, PO1993, PO2286, PO2297, PO2481, PUB049, PUB221, PUB291
renal fibrosis……………… TH-OR34, SA-OR55, PO3099, PO4015, PO4029, PO6263, PO6364, PO6065, PO6068, PO6059, PO1350, PO1405, PO1432, PO1903, PO2021, PO2030, PO2452, PO2544, PO2462, PO2467, PO2474, PO2476, PO2480, PO2482, PO2489, PO2493, PO2500, PO2502, PO2507, PO2510, PO2511, PO8085, PUB252, PUB325
renal function……………… TH-OR55, TH-OR67, SA-OR58, PO0227, PO0168, PO2555, PO3038, PO3495, PO4053, PO7028, PO817, PO1006, PO1109, PO1312, PO1831, PO1878, PO1880, PO1888, PO1957, PO2022, PO2203, PO2266, PO2432, PUB049, PUB063, PUB316, PUB321
renal function decline……………… TH-OR63, PO0378, PO0413, PO0737, PO0851, PO8888, PO9099, PO1765, PO1852, PO2278, PO2331, PO2395, PUB197
renal hemodynamics……………… FR-OR38, PO0364, PO0379, PO0764, PO1765, PO2038
renal hypertension……………… PO1769, PO1832, PO2486
renal injury……………… SA-OR10, SA-OR50, PO0008, PO0018, PO0027, PO0081, PO1113, PO1808, PO1821, PO2024, PO2190, PO2224, PO2228, PUB049, PUB293, PO3011, PO3031, PO3041, PO417, PO419, PO440, PO447, PO448, PO467, PO6032,
The TESTING Study: Steroids vs. Placebo in High Risk IgA Nephropathy

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Background: The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study assessed the effects of oral methylprednisolone compared to placebo on major kidney outcomes and safety in IgAN.

Methods: This investigator-initiated, double-blind randomized trial included people with IgAN, proteinuria ≥1 g/day and eGFR 20-120 mL/min/1.73m², following on major kidney outcomes and safety in IgAN. The TESTING study assessed the effects of oral methylprednisolone compared to placebo. Patients were randomized 1:1 to methylprednisolone (0.6-0.8 mg/kg/day, maximum 48 mg/day, for 2 months then weaning by 4 mg/day/month) or to matching placebo. In 2016, due to an excess of serious infections in the steroid arm, the methylprednisolone dose was reduced (0.4 mg/kg/day, maximum 32 mg/day, weaning by 4 mg/day/month) and pneumonia isvirine prophylaxis added. The primary endpoint was the composite of 40% eGFR decline or kidney failure (dialysis, transplantation or death due to disease) in those with pre-specified secondary and safety outcomes.

Results: In total, 503 participants (mean age 38 years, 39% female, mean eGFR 61.5 mL/min/1.73m², proteinuria 2.46 g/day) were randomised to methylprednisolone (257) or placebo (246), including 262 to the full dose and 241 to the reduced dose protocols. Over 4.2 years average follow up, methylprednisolone reduced the risk of the primary outcome by 47% (event rate 7.0 vs 11.8/100 patient years, HR 0.53, 95% CI 0.39-0.72, p < 0.0001), and ESKD by 41% (HR 0.59, CI 0.40-0.87, p=0.008). The reduction in risk was consistent across both dose protocols (p for heterogeneity 0.11): full dose HR 0.58 (95% CI 0.41-0.81), reduced dose HR 0.27 (95% CI 0.11-0.65). Serious adverse events were more frequent with steroids compared to placebo (28 vs 7 patients, p=0.0004), particularly with the full dose (22 vs 4, p=0.0003) vs the reduced dose regimen (6 vs 3, p=0.50).

Conclusions: Steroids reduce the risk of major kidney outcomes and kidney failure in people with high risk IgAN. The incidence of serious adverse events is increased mainly with high dose therapy. *joint first (JL MW)/senior authors (HZ VP)

Funding: Government Support - Non-U.S.

FR-OR62

Randomized Controlled Trial Comparing 3- vs. 6-Months Initial Prednisone Therapy in Young (<4-Year-Old) Children with Nephrotic Syndrome

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Background: While recent RCTs suggest no role for prolonged (>2-3 months) initial corticosteroid therapy in NS, subgroup analysis in 2 studies suggests its association with reduced subsequent relapses in children <2-4 yrs. This multicenter open-label trial examines the efficacy & safety of 3-months versus 6-months prednisone therapy during the first episode of NS in patients <4-yr-old [CTRI2015/06/005939; NCT01419726].

Methods: Following ethics approval & parental consent, 172 consecutive patients (<4 yr-old) were enrolled at onset of idiopathic NS during 2015-19. After 6-wk daily & 6-wk alternate day (AD) initial prednisone therapy, they were randomized (1:1) to either tapering prednisone on AD for 12-wk or no therapy. Relapses were treated with prednisone 2 mg/kg/d till remission, then on AD for 4-wk. Outcomes, based on intention-to-treat analysis during 2-yr follow up, include the proportion of patients with relapse or frequent relapses, time to first relapse, cumulative steroid dose & adverse effects. Based on a prior RCT, at 80% power & α=0.05, 78 patients were required per group to show 30% higher sustained remission with 6-mo therapy.

Results: Baseline features in the groups were similar (Fig 1). Despite trends favoring 6-mo therapy, proportions of patients in sustained remission & frequent relapses at 1- & 2-yr, time to relapse (HR 0.75, 95%CI 0.53-1.06) or frequent relapses (HR 0.78, 0.52-1.18), and relapse rates were similar (Fig 1, 2). The rates of adverse events were similar.

Conclusions: Prolonged initial prednisone therapy does not significantly alter the disease course in young children with NS.

Funding: Government Support - Non-U.S.
ILLUMINATE-C, a Single-Arm, Phase 3 Study of Lumasiran in Patients with Primary Hyperoxaluria Type 1 and CKD Stages 3b-5, Including Those on Hemodialysis

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Results: The most common adverse events (AEs) related to lumasiran were injection-site reactions, which were mild. There were no serious or severe AEs related to lumasiran nor deaths of patients that received lumasiran. There were no treatment discontinuations or study withdrawals.

Conclusions: Lumasiran resulted in substantial reductions in POx in PH1 patients with CKD 3b-5, with an acceptable safety profile through M6. Changes of this magnitude are directly related to the pathophysiology of oxalosis and reduction of POx is a relevant disease. As kidney function declines, oxalate elimination is compromised and plasma oxalate levels increase, which can lead to systemic oxalosis. In CKD stages 3b-5, elevated POx is directly related to the pathophysiology of oxalosis and reduction of POx is a relevant clinical trial endpoint. We present results from the 6-month primary analysis period of ILLUMINATE-C, a single-arm, phase 3 study to evaluate lumasiran, an RNAi therapeutic which inhibits oxalate production, in patients with PH1 and impaired kidney function.

Method: Key inclusion criteria: genetically confirmed PH1 diagnosis, eGFR ≥ 30 mL/min/1.73m², POx ≤ 108.4 (μmol/L) in cohort A and 108.4 (29.5) μmol/L in cohort B. In cohort A and B, respectively, lumasiran was administered IV daily for 3 weeks and then continued every 4 weeks until M6 (cohort A); percent change in pre-dialysis POx from baseline to M6 (cohort B).

Conclusions: Percutaneous fistulae created by interventionalists in the office based lab have provided durable access for hemodialysis patients for 5 years with a high rate of fistula use, and low rates of secondary procedures and complications.

Funding: Commercial Support - Medtronic

Table 1: Access Complications and Treatment

FR-OR66

ASCEND Program: Efficacy and Safety from ASCEND-D and -ND and Overall MACE Finding

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Background: The Apergna Studies in Chronic Kidney Disease (CKD): Erythropoiesis via a novel prolyl hydroxylase inhibitor Dopadaprest (ASCEND) phase 3 program investigated efficacy and safety of dopadaprest.

Methods: The program included 2 event-driven, cardiovascular outcomes trials (CVOTs) in non-dialysis (ASCEND-ND) and dialysis (ASCEND-D) patients comparing dopadaprest with conventional ESAs. Non-inferiority (NI) co-primary endpoints included mean change in hemoglobin (Hb) between baseline and evaluation period (avg over weeks 28-52; NI margin: -.075 g/dL) and time to first adjudicated major adverse CV event (MACE; NI margin: 1.25). Principal secondary endpoints, adjusted for multiplicity, included superiority assessments of MACE, MACE + thromboembolic events, MACE + hospitalization for heart failure and average monthly intravenous iron dose up to week 52 in ASCEND-D and time to progression of CKD in ASCEND-ND. Three smaller trials also reported adjudicated MACE but were not designed for formal MACE evaluation.

Results: 8169 patients were randomized across the 5 trials, with ~14,000 person-years (PY) of follow-up in CVOTs. The co-primary NI Hb objective was met in both CVOTs (adjusted mean treatment difference [95%CI]: ASCEND-D 0.19 [0.09-0.28] g/dL, ASCEND-ND 0.08 [0.03-0.13] g/dL). The co-primary NI MACE endpoint was also met (hazard ratio [95%CI]: ASCEND-D 0.83 [0.71-0.97], ASCEND-ND 0.80 [0.69-1.09]). No principal secondary endpoints met superiority. CVOT rates of treatment emergent adverse events were similar between dopadaprest and ESA groups. Figure shows program-level first adjudicated MACE rates per 100 PY (intent-to-treat); MACE rates for ASCEND-ND (N=614) were 5.1% vs 4.9% for dopadaprest and 7.2% vs 2.2% for placebo.

Conclusions: CVOTs demonstrated dopadaprest was non-inferior to ESA for Hb efficacy and MACE and was well-tolerated. CV safety was generally consistent across treatment groups in the other studies.

Funding: Commercial Support - Apylin Pharmaceuticals

FR-OR65

Long-Term Results of the Ellipsys Percutaneous Fistula for Hemodialysis

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Background: The Pivotal Multicenter Trial of Ultrasound Guided Percutaneous Arteriovenous Fistula (pAVF) Creation for Hemodialysis (Ellipsys Pivotal Trial) demonstrated the early safety and efficacy in a two-stage procedure with creation followed by maturation of proximal radial artery fistula for hemodialysis. The long-term outcomes through 5 years were evaluated to demonstrate fistula use, durability, and complications.

Methods: Prospective data from Ellipsys Pivotal Trial was combined with chart review to obtain a median follow-up of 50 (12 to 60) months. Review included fistula use, secondary procedures, and complications. The initial procedures and follow-up were performed in the office based lab (ORB) and later were moved to the OR for all procedures.

Conclusions: Those on Hemodialysis

Results: Patient characteristics are listed in Table 1. Kaplan-Meier (KM) analysis demonstrated secondary patency of 89.5%, 88.4%, 88.4%, 85.6%, and 82.0% at years 1-5. Functional patency was 97.5%, 97.5%, 97.5%, and 91.8% at years 1-4 after two-needle cannulation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

B2
FR-OR67
EMPEROR-Preserved: Empagliflozin and Outcomes in Heart Failure with a Preserved Ejection Fraction and CKD
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Background: In EMPEROR-Preserved, empagliflozin reduced cardiovascular death and heart failure hospitalizations and slowed the progressive decline in glomerular function in heart failure and a preserved ejection fraction (HFpEF), with or without diabetes. We explored the effect of empagliflozin on cardiovascular and kidney endpoints, across the spectrum of kidney function.

Methods: 5988 patients were randomized, of whom 3198 (53%) had prevalent chronic kidney disease (CKD) (eGFR<60ml/min/1.73m² or an UACR>300mg/g). The key outcomes were (1) a composite of cardiovascular death or hospitalization for heart failure, (2) total hospitalizations for heart failure, and (3) eGFR slope. The median follow-up was 26 months.

Results: Patients with prevalent CKD had a higher rate of CV and kidney events. Overall, empagliflozin reduced the risk of cardiovascular death and hospitalization for heart failure by 21% (p=0.003), reduced total hospitalizations for heart failure by 27% (p=0.001) and significantly slowed the yearly decline in eGFR (Difference: 1.36 mL/min/1.73 m² per year, p=0.001). In this present CKD subgroup analysis, all three benefits were observed, with a benefit of empagliflozin of -10.5 mL/min/1.73 m² in the CKD group (p<0.001) and significantly slowed the yearly decline in eGFR (Difference: 1.36 mL/min/1.73 m² per year, p<0.001) and significantly slowed the yearly decline in eGFR (Difference: 1.36 mL/min/1.73 m² per year, p<0.001) and significantly slowed the yearly decline in eGFR (Difference: 1.36 mL/min/1.73 m² per year, p<0.001).

Conclusions: In patients with HFpEF, empagliflozin reduced serious heart failure events and slowed the decline in glomerular function, regardless of the presence or absence of CKD and across the broad spectrum of baseline kidney function.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

FR-OR68
Chlorthalidone for Hypertension in Advanced CKD (CLICK): A Randomized Double-Blind Trial
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Background: Hypertension, a common risk factor for both cardiovascular disease and chronic kidney disease (CKD), remains poorly controlled, especially among patients with advanced CKD.

Methods: The chlorthalidone (CTD) in chronic kidney disease (CLICK) study was a placebo-controlled, double-blind, randomized control trial of CTD versus placebo in patients with advanced CKD. Here, patients with stage 4 CKD and poorly controlled hypertension as confirmed by 24-hour ambulatory BP monitoring were randomly assigned to either placebo or CTD 12.5 mg daily in a 1:1 ratio stratified by prior loop diuretic use. The primary end point was the change in 24-hour systolic ambulatory BP from baseline at 12 weeks and was multiply imputed for missing data. Secondary outcome measures were the change from baseline to 12 weeks in the following measures: urine albumin to urine creatinine ratio, NT-pro BNP, plasma renin, plasma aldosterone, and total body volume. Long term follow up was planned for 3 years. An NHLBI-appointed DSMB had trial oversight.

Results: Of the 160 randomized, 140 patients (88%) completed the 12 weeks of double-blind exposure phase. Mean 24-hour ambulatory BP at randomization was 140.1 (8.1)/72.8(9.3) mmHg in the placebo group and 142.6 (8.1)/74.6 (10.1) mmHg in the CTD group. The adjusted change from baseline to 12 weeks in 24-hour systolic blood pressure was -0.5 (95% CI, -3.5 to 2.5) mmHg in the placebo group and -11.0 (95% CI, -13.9 to -8.1) mmHg in the CTD group. The between group difference was -10.5 (95% CI, -14.6 to -6.8; p<0.0001) mmHg. Compared to placebo, the urine albumin to urine creatinine ratio in the CTD group at 12 weeks was 50% lower (95% CI, 37% to 60%). CTD also induced changes in NT-proBNP, renin, aldosterone and total body volume were directionally consistent with a diuretic effect. Following randomization, hypokalemia, reversible increases in serum creatinine, hyperglycemia, dizziness, and hyperuricemia occurred more frequently in the CTD group.

Conclusions: In summary, this trial showed that treatment with CTD could effectively treat poorly controlled systolic hypertension in patients with advanced CKD. The reduction in albuminuria points to an early effect of target organ protection. (funded by National Institutes of Health NHLBI R01 HL126903; registration number NCT02841280)

Funding: Other NIH Support - NHLBI

PO2522
Activated Vitamin D for the Prevention of AKI in Critically Ill Patients
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Background: Decreased circulating levels of active vitamin D metabolites, including 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D), are common in critically ill patients, and lower levels are independently associated with a higher risk of AKI. Administration of 25D and 1,25D attenuates AKI in animal models. Randomized trials of vitamin D in critically ill patients have focused on inactive precursors (e.g., cholecalciferol), which may not be efficiently converted into 25D and 1,25D in this setting.

Methods: We conducted an NIH-funded, 3-arm, double-blind, randomized clinical trial using high doses of 25D and 1,25D in 150 critically ill patients at high risk of AKI. Patients were randomly assigned in a 1:1:1 ratio to receive 25D (oral calcifediol, 400μg on day 1 and 200μg on days 2-5), 1,25D (oral calcitriol, 4ug daily for 5 days), or placebo.

Results: Among the 150 patients enrolled, the median age was 65 years (IQR, 52-72), 61% were male, 83% were intubated, and 57% were receiving vasopressors at randomization. The median time from ICU admission to randomization was 1 day (IQR, 0-7). Median levels of 25D and 1,25D at randomization were 17 ng/ml (IQR, 10-26) and 27 pg/ml (IQR, 18-39), and increased to 57 ng/ml (IQR, 53-67) and 91 pg/ml (IQR, 66-122) in the 25D and 1,25D groups, respectively. Neither the primary nor secondary endpoints differed between groups (Table). Longitudinal plasma and urinary KIM-1 levels were also similar between groups. No safety concerns were identified.

Conclusions: Administration of activated vitamin D metabolites did not improve renal outcomes among critically ill patients.

Funding: NIDDK Support
PO2523
SCD Treatment in COVID-19 ICU Patients with ARDS and AKI Is Safe and May Improve Clinical Outcomes
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Background: ICU patients with COVID-19 with acute respiratory distress syndrome (ARDS) on mechanical ventilation (MV) and acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) have very high mortality rates. Elevation of certain inflammatory mediators, including IL10 and soluble IL1 receptor-like 1 (sST2), predict mortality in COVID-19 patients and declines as patients recover. Previous data have shown that treatment with a selective cytopheretic device (SCD) improves clinical outcomes in ARDS and severe AKI by removing proinflammatory leukocytes from circulation and reducing plasma levels of inflammatory cytokines. The aim of this feasibility study was to evaluate the safety and early efficacy of SCD treatment (Txs) in ICU COVID-19 patients with ARDS on MV and AKI requiring CRRT.

Methods: 22 subjects were enrolled and treated with SCD for ≤ 10 days. 5 patients were treated ≤ 96 hours due to family's request for withdrawal of care. Patients were previously treated with remdesivir and corticosteroids. All but one patient were on both MV and CRRT with 10 patients on extracorporeal membrane oxygenation (ECMO). A subgroup of 8 patients was further evaluated with plasma inflammatory biomarkers and cell sorting/cytometric analysis (CSCA) of circulating neutrophils and monocytes. Clinical outcomes of SCD-treated patients were compared to untreated control patients on CRRT and mechanical ventilation in a contemporaneous, prospective observational data set (CRRTnet).

Results: Patients completed the study between September 2020 and July 2021. Mean age was 53 ± 17 years (19-79). No device-related serious adverse events were reported. 60-day mortality in the SCD treated group was 11/22 (50%) vs 11/13 (85%) in the control group. CSKA demonstrated SCD removed the most activated circulating neutrophils (CD11b, CD10) and monocytes (CD11b, CD14). SCD Txs reduced baseline plasma levels of IL10 (12 ± 9 pg/ml to 2 ± 1, p < 0.02) and sST2 (212 ± 70 pg/ml to 88 ± 74, p < 0.02), as well as reducing plasma IL6 and MCP (Monocyte Chemotactic Protein)-1 levels.

Conclusions: SCD treatment is safe in ICU COVID-19 patients with ARDS on MV and AKI requiring CRRT. In this feasibility study, mortality rate was substantially lower than a concurrent control group, suggesting clinical benefit.

Fundig: Commercial Support - SeaStar Medical, Inc., Private Foundation Support

PO2524
Effect of Clinical Decision Support with Audit and Feedback for Prevention of AKI in Coronary Angiography and Intervention: Stepped Wedge Cluster Randomized Trial
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Background: Contrast-associated acute kidney injury (CA-AKI) is a common complication of coronary angiography and percutaneous coronary intervention (PCI). We evaluated whether the incidence of CA-AKI was reduced with an intervention including clinical decision support with audit and feedback.

Methods: In this cluster-randomized, stepped-wedge trial conducted in Alberta, Canada, we randomly assigned all invasive cardiologists to various start dates for an intervention that included education, point-of-care computerized clinical decision support on contrast volume and IV fluid targets, and repeated audit and feedback related to these processes for CA-AKI prevention. The eligible study population included adults ≥ 18 years of age, not receiving dialysis, with a predicted risk of CA-AKI >5%, who received non-emergency coronary angiography or PCI. The primary outcome was incidence of AKI based on the KDIGO serum creatinine criteria. Analyses were performed according to the intention-to-treat principle, using mixed-effect models to account for clustering in the data.

Results: Of 34 physicians randomized, 3 retired prior to randomization, and the remaining 31 received the intervention. There were 7,687 procedures performed in 6,449 eligible patients; mean (SD) age 70.2 (10.7) years, 2,292 (32.3%) female, mean (SD) eGFR 62.7 (22.4) mL/min/1.73m². The proportion of procedures where the desired contrast volume limit was exceeded was reduced from 41.0% to 29.2% (p < 0.01), while the proportion who received hemodynamically guided IV fluids increased from 35.3% to 42.0% (p < 0.01) with the intervention. The incidence of CA-AKI was significantly reduced, from 9.2% (280 events/3,036 procedures) before the intervention to 8.2% (334 events/4,051 procedures) with the intervention (time adjusted odds ratio, 0.74; 95% CI, 0.59 to 0.94). There was no statistical evidence of effect modification by age, sex, comorbidity, or baseline CA-AKI risk.

Conclusions: An intervention combining education, clinical decision support, and audit and feedback resulted in less contrast dye use, greater intravenous fluid administration, and reduced the incidence of CA-AKI following coronary angiography and PCI.

Fundig: Government Support - Non-U.S.
PO2528

Association of Urine Albumin-to-Creatinine Ratio and Its Early Change with Cardiorenal Outcomes in FIDEILIO-DKD: A Mediation Analysis

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Background: The selective, nonsteroidal mineralocorticoid receptor antagonist finerenone slowed chronic kidney disease (CKD) progression and improved cardiovascular (CV) outcomes in patients with CKD and type 2 diabetes (T2D) in FIDEILIO-DKD (NCT02540993). Previous studies have shown that treatment-induced urine albumin-to-creatinine ratio (UACR) reduction correlates with kidney and CV benefits. Here, we investigate the association of UACR and its early change with the magnitude of cardiorenal protection.

Methods: Patients (N=7,654) with T2D, UACR ≥ 5500 mg/g and estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73 m² receiving optimized renin–angiotensin system blockade were randomized 1:1 to finerenone or placebo. Key outcomes included a kidney composite of time to kidney failure, sustained ≥ 40% or ≥ 57% eGFR drop, or death; and a CV composite of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Outcomes were assessed using cubic-basis splines including UACR at baseline and change in UACR from baseline to month 4 as continuous variables. Mediation analyses were performed to determine the proportion of change in UACR to month 4 contributing to the kidney and CV benefits of finerenone.

Results: Fierenerone was associated with a 31% greater reduction in the UACR from baseline to month 4 than placebo (ratio of least-squares mean change from baseline, 0.69; 95% confidence interval 0.66–0.71). Overall, the risk of adverse kidney and CV outcomes increased as UACR at baseline increased. Reduction in UACR from baseline to month 4 was also associated with a reduction in risk for kidney outcomes. Mediation analyses indicated a variable proportion of the kidney and CV benefits observed with finerenone could be explained by early change in UACR.

Conclusions: Fenerone resulted in early reductions in UACR in patients with T2D and CKD that are associated with its beneficial effects on kidney and CV outcomes. We will discuss early changes in UACR as a biomarker of subsequent finerenone-associated cardiorenal benefit.

Funding: Commercial Support - Bayer AG

PO2529

Dapagliflozin and Kidney Outcomes in Hospitalized Patients with COVID-19 Infection: Results from the DARE-19 Randomized Controlled Trial

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Background: Hospitalized patients with COVID-19 infection are at high risk of acute kidney injury (AKI) and renal replacement therapy, especially in the presence of chronic kidney disease (CKD). The DARE-19 trial showed that in hospitalized patients with COVID-19, treatment with dapagliflozin (DAPA) vs placebo resulted in numerically fewer patients experiencing organ failure or death, although these differences were not

PO2526

REDUX: A Multicenter, Open-Label Study of DM199 (Recombinant Human Tissue Kallikrein-1) in Patients with Stage 2 or 3 CKD

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Background: DM199 is a recombinant form of the endogenous human tissue kallikrein-1 protein (KLK1) that by selectively releasing bradykinin-mediated nitric oxide, prostaglandins and other anti-inflammatory mediators to increase renal blood flow, and reduce inflammation, oxidative stress, and fibrosis in the kidney and elsewhere. The safety, efficacy, pharmacokinetics, and pharmacodynamics of DM199 is being evaluated in an open-label, Phase 2 study of patients with chronic kidney disease (CKD).

Methods: Here, enrolling three cohorts of patients all with stage 2 or 3 CKD: 1) non-diabetic African Americans with hypertension (AA/CKD); 2) patients with type 2 diabetes mellitus with hypertension (DKD). Patients were assigned to receive subcutaneous DM199 2 or 5 mcg/kg twice weekly for 95 days. Primary endpoints were safety and tolerability, kidney function (eGFR, urine:albumin creatinine ratio [UACR], blood pressure), and plasma and urine pharmacokinetics of DM199 (and KLK1).

Results: At an interim analysis conducted June 2021, 62 patients had completed the study, and data were available for 56 patients, 12 in the AA/CKD cohort, 16 in the IgAN cohort, and 28 in the DKD cohort. Results are in the Table. DM199 was well tolerated across all cohorts, with no DM199 related severe adverse events (AEs) or discontinuations due to drug-related AEs. AEs were generally mild to moderate in severity, with the most common being local injection site irritation that resolved.

Conclusions: These data provide clinical validation of the meaningful biologic activity of the recombinant KLK1 (DM199) and support the potential of achieving clinical benefit in patients with CKD. Enrollment is continuing in the AA/CKD and IgAN cohorts.

Funding: Commercial Support - DiaMedica Therapeutics, Inc.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
statistically significant. We performed a pre-specified secondary analysis of DARE-19 to determine the efficacy and safety of DAPA on kidney outcomes in the overall population and by CKD status.

**Methods:** The DARE-19 trial randomized 12,501 hospitalized patients (231 [18.5%] had eGFR <60 mL/min/1.73m2) with COVID-19 and cardiometabolic risk factors to DAPA or placebo. Dual primary outcomes (time to new or worsened organ dysfunction or death, and a hierarchical composite endpoint of recovery [change in clinical status by Day 30]), and the specific kidney outcome (composite of AKI, renal replacement therapy or death), as well as safety were assessed in patients with baseline eGFR <60 and ≥60 mL/min/1.73m2.

**Results:** The effect of DAPA vs placebo on the primary prevention outcome (hazard ratio [HR] 0.80 [95% CI 0.58, 1.10]) and primary recovery outcome (win ratio 1.09 [95% CI 0.79, 1.22]) was consistent across eGFR subgroups (p for interaction 0.36 and 0.46, respectively). The effect on the composite kidney outcome (HR 0.74 [95%CI 0.5 0.50, 1.07]) was also consistent in eGFR subgroups (p for interaction 0.44). There were numerically fewer AKI events with DAPA in patients with eGFR<60 mL/min/1.73m2 (HR 0.71 [95% CI 0.29, 1.77]) and ≥60 mL/min/1.73m2 (HR 0.69 [95% CI 0.37, 1.29]). DAPA was well tolerated in patients with eGFR<60 and ≥60 mL/min/1.73m2.

**Conclusions:** The effects of DAPA on primary and secondary outcomes in hospitalized patients with COVID-19 were consistent in those with without CKD. DAPA was well tolerated and did not increase the risk of AKI in patients with/without CKD.

**Funding:** Commercial Support - AstraZeneca

**PO2530**

Maintaining Operational Excellence During the COVID-19 Pandemic in the FLOW Trial

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**Background:** The FLOW trial is a multicenter, international, randomized, phase 3b kidney outcomes trial of once-weekly subcutaneous semaglutide vs placebo, both added to standard-of-care, in >3,500 people with type 2 diabetes and chronic kidney disease. The trial is guided by a steering committee with academia and industry representatives and a global expert panel (GEP). The coronavirus disease 2019 (COVID-19) pandemic has presented major challenges for running clinical trials, with restrictions for trial sites impacting recruitment and retention. Once the extent and hazards of COVID-19 were apparent, regular impact assessments were done to quickly identify and mitigate challenges to the conduct of the trial. Here, we report the timing of mitigation strategies in the FLOW trial and the relationship to recruitment during the pandemic.

**Methods:** The primary focus was to ensure participant and staff safety and no undue risk of COVID-19 exposure, as well as data integrity, recruitment and retention. These aims were met by implementing protocol amendments, guidance documents for trial sites and local support from GEP members, through strategies such as replacing face-to-face visits with phone and home visits, remote monitoring, alternative trial drug dispensing and allowing for co-participation in COVID-19 trials (Figure).

**Results:** After the mitigation strategies were employed in response to the COVID-19 pandemic, the FLOW trial recruitment was completed according to schedule (Figure). To date, no participants have withdrawn from the FLOW trial due to COVID-19.

**Conclusions:** After the rapid identification and implementation of mitigation strategies and efforts of the steering committee and GEP, the FLOW trial successfully recruited the planned number of participants on time and avoided withdrawals due to COVID-19.

**Funding:** Commercial Support - Novo Nordisk A/S

**PO2531**

Finerenone and Kidney Outcomes in Patients with CKD and T2D: Results from FIDELITY

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**Background:** FIDELITY, a prespecified meta-analysis of FIDELIO-DKD and FIGARO-DKD, evaluates the efficacy and safety of finerenone across a spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).

**Methods:** FIDELITY combines individual patient data from FIDELIO-DKD (NCT02549093) and FIGARO-DKD (NCT02545049). Eligible patients were adults with T2D and CKD (baseline albumin-to-creatinine ratio [UACR] ≥30–500 mg/g and estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m2, or UACR ≥3000 mg/g and eGFR <25 mL/min/1.73m2), treated with optimized renin–angiotensin system blockade. Efficacy outcomes included a composite kidney outcome of time to first onset of kidney failure (end-stage kidney disease [ESKD] or sustained eGFR <15 mL/min/1.73m2), sustained ≥5% decrease in eGFR from baseline over ≥4 weeks, or renal death.

**Results:** In 13,026 patients, over 3 years’ median follow-up, finerenone reduced the risk of the kidney composite outcome by 23% vs placebo (HR=0.77; 95% CI 0.67–0.88; p<0.0002); consistent benefits were observed across baseline eGFR and UACR subgroups (P=0.62 and 0.67, respectively). Compared with placebo, finerenone led to a nominally significant reduction in the incidence of all nonfatal components of the kidney composite outcome, including a 20% lower risk of ESKD (chronic dialysis or kidney transplant; HR=0.80; 95% CI 0.64–0.99; P=0.04). Finerenone caused an initial drop in eGFR vs placebo (least-squares [LS] mean change in eGFR slope from baseline to month 4, –3.3 vs –1.0 mL/min/1.73m2) but slowed long-term eGFR loss (LS mean change in eGFR slope from month 4 onwards, –2.5 vs –3.7 mL/min/1.73m2/year). The incidence of adverse events was similar between groups. The incidence of permanent discontinuation due to hyperkalemia in finerenone and placebo recipients with an eGFR <60 mL/min/1.73m2 was 2.4% and 0.8%, respectively, and 0.6% and 0.3% in those with an eGFR ≥60 mL/min/1.73m2.

**Conclusions:** FIDELITY demonstrates robust kidney benefits and safety of finerenone in patients with T2D across the spectrum of CKD severity.

**Funding:** Commercial Support - Bayer
PO2532
ACCESS (NCT02513303): A Phase 3 US Multicenter Randomized Controlled Trial Evaluating Efficacy of a Perivascularly Delivered Sirolimus Formulation (Sirogen™) for Improving Hemodialysis AVF Outcomes
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Background: Lack of a prophylactic therapeutic for improving AV Fistula Suitability for Dialysis (FSD) is an unmet need. Sirolimus delivered locally to the vessel wall is a clinically proven anti-proliferative. Advancing age, female gender & comorbidities like coronary artery disease (CAD) are known risks for AVF maturation.
Methods: The Full Analysis Set (FAS) included 243 pts randomized 1:1; 125 Sirogen 118 Controls; 174 ESRD 89 CKD; 205 RCF 174 BCF. End points: Clinical FSD: AVF use with 2 needles with mean Qb a≥ 300 mL/min (2N/300) for at least 2/3 of the HD sessions during a 30-day period starting day 150 (FSD6; Primary Endpoint) or day 330 (FSD12). Ultrasound FSD: outflow vein diameter ≥ 500 ml/min; criteria used if CKD pt. was not on HD by day 150 or ≤ 330. Secondary Patency (SP); Fistula survival without abandonment; Fistula Maturation (FM); AVF use for 3 consecutive 2N/300 HD sessions.
Results: Age subgroup analysis provides explanation supported by data for endpoint results shown in Table 2:3rd of randomized pts were <65y (lower risk). In ESRD pts a clear evidence of Rx effect (Figs 1,2); RCF outcomes were even more compelling. Exceptional control performance in ≥65y group masked treatment effect. No evidence of Rx failure. No safety concerns.
Conclusions: 1. No differences in prespecified endpoints 2. Demographic differences & risk issues (known favored controls) motivated a post hoc: age subgroup analysis. ≥65y; Control overperformance (not Rx failure) negated endpoint differences & influenced overall outcomes b.≥65y: Maturation Benefit (FM) is significant & durable (FSD12, SP) 3. Confirmatory Trial is planned
Funding: Commercial Support - Vascular Therapies, Inc

PO2533
Incremental HD in the US: A Multicenter Pilot Controlled Trial
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Background: Incremental HD—twice-weekly initiation followed by thrice-weekly HD—is uncommonly prescribed in the US. We conducted a pilot trial to assess the feasibility and safety of incremental-start HD.
Methods: Adults with eGFR ≥ 500mL/day initiated on maintenance HD at 14 centers were randomly assigned to twice-weekly HD and adjuvant pharmacologic therapy (loop diuretics, sodium bicarbonate, patiromer) for 6 weeks, then transitioned to thrice-weekly HD (incremental HD) (n=23) vs continued thrice-weekly HD (conventional HD) (n=25). Intervention was embedded in usual care.
Results: Adherence to assigned HD schedules and serial timed urine collection was 96% and 100%, respectively, in both groups. Two patients in incremental group switched to thrice-weekly HD in ≤6 weeks (Figure). There were fewer hospitalizations and deaths in incremental group (Table 1). Between-group differences in % change from baseline to week 26 in urine volume and renal average area and creatinine clearance favored incremental HD (Table 2).

PO2534
A Randomized, Double-Blind, Phase 2 Study to Evaluate the Tolerability, Feasibility, and Efficacy of AKST1210 in Patients on Hemodialysis with ESRD and Cognitive Impairment
Background: Cognitive impairment is frequently observed in many end-stage renal disease (ESRD) patients undergoing hemodialysis (HD). Since this protein is not effectively cleared with standard HD, beta-2 microglobulin (b2M) is highly elevated in ESRD patients and data in mice has shown that b2M is a potential driver of cognitive impairment and synapse loss. Based on robust preclinical data, a clinical study was initiated to assess safety, tolerability, and feasibility of utilizing AKST1210, an extracorporeal b2M-selective adsorbent column, during HD in patients with ESRD and cognitive impairment (ESRD-CI).
Methods: The study inclusion criteria were adults ≥40 years of age on HD for ≥12 months and a Montreal Cognitive Assessment (MoCA) score ≥16 and ≥23. Participants were randomized 1:1 to receive HD 3 times a week for 12 weeks with either AKST1210 (escalating size every 4 weeks) or no column. The primary objective was to assess the safety of AKST1210 as evaluated by the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Secondary objectives included tolerability of procedures as assessed by participant compliance and retention as well as changes from baseline in b2M levels, activities of daily living (ADL), and cognitive assessments.
Results: Of 36 patients screen ed, 22 were randomized, 20 completed through end of treatment, and 19 completed the study. Thirty-four of 36 patients screened met the MoCA eligibility criteria. Preliminary review of safety data indicate AKST1210 is safe and well tolerated in this study population based on a low incidence of TEAEs and SAEs, adherence to study procedures, and completion of the treatment period in greater than 90% of participants. Analysis of the secondary and exploratory endpoints related to change from baseline in cognitive function, ADL, and b2M levels will be presented.

Figure 1

Table 1

Table 2

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Assessment and treatment of cognitive impairment in patients with ESRD remains an unmet need. Treatment with AKST1210 provides a safe and tolerable intervention targeting removal of B2M, a potential driver of cognitive impairment. Further investigation with AKST1210 to better understand efficacy related to cognitive impairment, ADL, and quality of life is warranted.

Funding: Commercial Support - Alkahest, Inc.

PO2535
Enhancing Decongestion in Cardiorenal Syndrome by Renal Negative Pressure Diuresis: A First in-Human Experience
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Background: Inadequate decongestion is the driver of adverse outcomes in acute decompensated heart failure (ADHF). Accumulating data points to renal venous congestion as the key mechanism underlying cardiorenal syndrome and diuretic resistance. Herein, we present the initial experience with a novel device that utilizes negative pressure in the renal pelvis to enhance diuresis (i.e. renal negative pressure diuresis [rNPD]).

Methods: rNPD involves endoscopic delivery of a ureteral catheter. Its proximal portion is placed in the renal pelvis to deliver controlled negative pressure via a specially designed vacuum pump. Patients with ADHF and diuretic resistance underwent rNPD for 24 hours. Several parameters including GFR, urine output, and natriuresis were measured 24 hours before and 24 hours after rNPD (72-hour study period).

Results: The current proof-of-concept study includes 3 patients from 2 centers meeting strict inclusion and exclusion criteria. Mean serum creatinine levels were 1.86 ± 0.82 mg/dL before and 1.82 ± 0.7 mg/dL after intervention respectively. rNPD resulted in a significant increase in natriuresis without any notable adverse effect. Impressive improvement in net negative fluid balance associated with exponential increase in urinary sodium excretion (from 148 ± 36 mmol/24 hours before and 24 hours after rNPD (72-hour study period).

Conclusions: After successful animal studies, this proof-of-concept study is the first in-human experience confirming the salutary impact of applying negative pressure in the renal pelvis of patients with ADHF and diuretic resistance. rNPD resulted in an exponential increase in urinary sodium excretion (from 148 ± 36 mmol/24 hours before and 24 hours after rNPD (72-hour study period).

Funding: Commercial Support - 3ivelabs

PO2536
Iptacopan, a Novel Oral Complement Factor B (FB) Inhibitor, Significantly Reduces Proteinuria and C3 Deposit Scores in Native and Transplanted Kidneys C3 Glomerulopathy (C3G) Patients
Edwin K. Wong, Carla M. Nester, Teresa Caverso escribano, Alexandre Karras, Moglie Lequintrec-Domente, Liz Lightstone, Urs; Goenburger, Maria Jose Soler, Andrea Biondani, Frederique Chaponot, Kenneth M. Kulmatycki, Julie M. Milojevic, Prasanna Kumar Nidamarty, Nicholas Webb, Guido Junge, Giuseppe Remuzzi, Freeman Hospital, Newcastle upon Tyne, United Kingdom; University of Iowa Hospital and Clinics, Iowa, IA; Hosp 12 de Octubre, Madrid, Spain; AP-HP, Hôpital Européen Georges Pompidou, Paris, France; Hôpital Lapeyronie, Montpellier, France; Imperial College Healthcare NHS Trust, London, United Kingdom; Nephrology Department Hospital Universitario Vall d’Hebron, Barcelona, Spain; Novartis Healthcare Pvt Ltd, Hyderabad, India; NIBR, Basel, Switzerland; Centro Ricerche Cliniche per Malattie Rare Aldo e Cele Daccò Villa Camozzi, Bergamo, Italy; Universitätsklinikum Essen, Essen, Germany.

Background: C3G is a rare, inflammatory KD caused by genetic mutations or auto-AB that dysregulate the complement system. With no approved therapies, progression to ESRD is frequent. Iptacopan is a new, highly selective oral LMW inhibitor of FB, a key complement alternative pathway (AP) protease. We report final Phase 2 data [NCT03832114] for iptacopan in pts with native or recurrent C3G post kidney Tx.

Methods: Adults with biopsy-proven (Bx), native (CoA) or recurrent C3G post KTx (CoB) received iptacopan for 12 wks (W). CoA had proteinuria >1g/24h despite ACEi/ARB, and all had low C3 levels. Primary endpoints (pEP) were reduction in UPCR from baseline (BL) to W12 for CoA; change in C3 Deposit Score (DS) for CoB. Pts were invited to continue iptacopan in a long-term extension trial [NCT03955445].

Results: All pts (N=16/11 in CoA/B) completed the trial. BL mean age 26.1/34.5 yrs; geo-mean UPCR (24h) 0.9/36.2 g/mol; mean eGFR 70.1/52.2 mL/min in CoA/B; median C3 DS 3.0 in CoB. Iptacopan was well tolerated without any drug-related serious AE. CoA pEP met with -45% in UPCR from BL to W12 (p=0.0003) [Fig 1A]. CoB pEP met with significant reduction in C3 DS in kidney Bx from BL to W12 (p=0.0313) [Fig 1B]. A profound and sustained inhibition of the AP [Fig 1C] and normalization of C3 levels were observed [Fig 1D]. eGFR was stable with mean change from BL to W12 of +1.04 mL/min.

Conclusions: Treatment with iptacopan 200 mg bid in patients with native or recurrent C3G was well tolerated and resulted in statistically significant and clinically important reduction of UPCR, normalization of C3 levels, stabilization of eGFR, and significant reduction in histologic C3 DS in follow-up kidney Bx. Iptacopan is now tested in a pivotal Phase 3 trial APPEAR-C3G [NCT04817618].

Funding: Commercial Support - NCT03832114 Phase 2 trial sponsored by Novartis Institutes for Biomedical Research (NIBR)
PO2537

Prescribed Water Intake in Autosomal Dominant Polycystic Kidney Disease

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Background: Arginine vasopressin (AVP) promotes kidney cyst growth in autosomal dominant polycystic kidney disease (ADPKD). Increasing water intake to reduce urine osmolality and AVP release is hypothesized to slow kidney cyst growth in ADPKD.

Methods: In this multi-center, open-label, parallel-arm randomized controlled 3-year trial adults with ADPKD and Mayo Subclass 1B to 1E and an estimated glomerular filtration rate (eGFR) of ≥50 mL per minute per 1.73 m² were randomized to either ad libitum water intake (92 patients) or prescribed water intake (92 patients). Over 3 years the mean treatment differences between the ad libitum water and prescribed water intake groups for 24-hour urine osmolality and 24-hour urine volume were -91 mOsm/kg (95% CI –127 to -54 mOsm/kg; P<0.01) and 0.6L/day (95% CI 0.4 to 0.9L/day; P<0.01) respectively. The proportion of patients with 24-hour urine osmolality <300 mOsm/kg for >50% of timepoints was 52%. There was no difference in the percentage annualized rate of change in Ht-TKV between the groups (ad libitum water intake irrespective of urine osmolality. The primary endpoint was the annualized rate of change in the height-corrected total kidney volume (Ht-TKV).

Results: One hundred and eighty-four patients, with a mean 24-hour urine osmolality of 423±178 mOsm/kg and median 24-hour urine volume of 2.3L/day (IQR: 1.8-3.1L/day) at baseline, were randomized to either ad libitum water intake (92 patients) or prescribed water intake (92 patients). Over 3 years the mean treatment differences between the ad libitum water and prescribed water intake groups for 24-hour urine osmolality and 24-hour urine volume were -91 mOsm/kg (95% CI –127 to -54 mOsm/kg; P<0.01) and 0.6L/day (95% CI 0.4 to 0.9L/day; P<0.01) respectively. The proportion of patients with 24-hour urine osmolality <300 mOsm/kg for >50% of timepoints was 52%. There was no difference in the percentage annualized rate of change in Ht-TKV between the groups (ad libitum water intake irrespective of urine osmolality. The primary endpoint was the annualized rate of change in the height-corrected total kidney volume (Ht-TKV).

Conclusions: Prescribed water intake compared to ad libitum water intake resulted in improved urine osmolality and reduced Ht-TKV in ADPKD patients compared to ad libitum water intake. However, further research is warranted in a larger population to confirm these findings.

Funding: Commercial Support - Danone Research, Government Support - Non-U.S. Commercial Support - Danone Research, Government Support - Non-U.S.

PO2539

PHYOX2: Nedosiran Reduced Urinary Oxalate Excretion in Patients with Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH) is a family of 3 ultra-rare genetic disorders characterized by hepatic oxalate overproduction leading to hyperoxaluria, recurrent calcium oxalate kidney stones, nephrocalcinosis, and often, kidney failure. Nedosiran is an investigational RNA interference (RNAi) therapy that reduces overproduction of oxalate by inhibiting hepatic dehydrogenase (LDH). Results from PHYOX2, the pivotal trial of nedosiran in 35 participants with PH1 or PH2 are reported here.

Methods: See Table

Results: PHYOX2 achieved its primary and key secondary endpoints. Nedosiran resulted in a 57.5% greater daily average reduction in urinary oxalate (Uox) excretion AUC (based on D90 to D180 AUC) compared to placebo (P<0.0001). Among participants given nedosiran, 50% achieved and sustained normal or near-normal Uox at 2 or more consecutive visits after D90 compared to 0% given placebo (P=0.0025). Uox was similarly reduced in the PH2 cohort (Figure; post hoc analysis). The results in the PH2 cohort (5 nedosiran, 1 placebo) were inconsistent; only 2 out of 5 participants given nedosiran showed reduction in Uox between D90 and D180. The most common AEs were mild, self-resolving injection site reactions. There were 3 SAEs (1 in nedosiran; 2 in placebo).

Conclusions: Nedosiran was well-tolerated and resulted in a clinically and statistically significant sustained reduction in Uox excretion compared to placebo, with robust efficacy in the PH1 subtype. The heterogeneity of response in the smaller PH2 cohort was incongruent with prior clinical experience and warrants further investigation.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc.
Telitacicept in Patients with IgA Nephropathy and Persistent Proteinuria (A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of Telitacicept at Week 26 vs Placebo at Week 26) in Former Placebo Group

**Background:** Telitacicept is a novel fusion protein composed of transmembrane activator and CAML stimulator (BLyS) and a proliferation-inducing ligand (APRIL). This phase II study evaluates efficacy and safety of telitacicept compared with placebo, when added to standard therapy in patients with IgAN at high risk for progression.

**Methods:** In this randomized, double-blind, placebo-controlled trial, we enrolled patients with proteinuria ≥ 0.75g/day despite optimal supportive care, who were randomized to receive subcutaneous telitacicept at 160mg, 240mg or placebo weekly for 24 weeks. The primary endpoint was a change in 24-hour proteinuria at week 24; key secondary endpoints included change in eGFR.

**Results:** Overall 44 participants were randomized in this study: placebo (14) and telitacicept (160g (16) and 240g (14)). A consistent, dose-dependent reduction in serum IgA (Figure 1A). IgA and IgM were observed through Week 24. Telitacicept therapy was associated with a 49% decrease from baseline in mean proteinuria (change in proteinuria vs placebo -0.88; 95% CI: -1.57 to -0.20; p=0.013) received 240mg, and 25% reduction in eGFR at Week 13 and statistically significant reductions were also observed at Week 9 and in the extension phase and were followed for a median of 22 months. Patients received median 1 course of 12 weekly doses of narsoplimab per year (range 0.7–2.5 courses), with 58% (7/12) receiving ≤ 1 course per year. eGFR rate of decline was 5.2 (±1.2) mL/min/yr vs 8.6 (±3.7) mL/min/yr in the Leicester IgAN control cohort, suggesting better eGFR stability in the patient population. Over 3 years, eGFR improved in 25% (3/12) of patients. UPE decreased 38% from baseline through the follow-up period. Narsoplimab was well tolerated with no treatment-related serious adverse events reported.

**Conclusions:** In this Phase 2 study, narsoplimab was well tolerated. Treatment in patients with severe IgAN resulted in proteinuria reduction and better renal protection via eGFR stability relative to a matched comparator group.

**Funding:** Commercial Support - Omeros Corporation

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**PO2541**

**Long-Term Phase 2 Efficacy of the MASP-2 Inhibitor Narsoplimab for Treatment of Severe IgA Nephropathy**

Richard A. Lafayette,1 Kevin Carroll,2 Jonathan Barratt.1

On behalf of the ALC Steering Committee 'Stanford University, Stanford, CA; 2KJC Statistics Ltd., Cheshire, United Kingdom; 1University of Leicester, Leicester, United Kingdom.'

**Background:** IgA nephropathy (IgAN) is a glomerular disease in which the lectin pathway of complement is activated following mesangial deposition of IgA immune complexes. Narsoplimab (OMS721) inhibits mannose-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway.

**Methods:** A staged Phase 2 study (NCT02682407) enrolled adult patients with severe IgAN. Substudy 1 was a single-arm open-label study of 12 weekly IV infusions of narsoplimab and tapered corticosteroids. In a substudy 2, corticosteroid-free patients were randomized 1:1 to receive weekly IV narsoplimab or vehicle infusions for 12 weeks followed by open-label extension. The primary endpoint was safety and tolerability of narsoplimab. Key secondary endpoints were 24-hour urine protein excretion (UPE) and estimated glomerular filtration rate (eGFR) assessed by time-weighted average regression analysis up to 35 months follow-up. Patients from the Leicester Renal Unit IgA Nephropathy Registry with similar disease burden and matched baseline UPE and eGFR values were used as the comparator group.

**Results:** This high-risk population with advanced IgAN at enrollment had a median disease duration of 6.9 years (range 0.4–27.5). Baseline risk factors included hypertension (10/12, 83%), obesity (7/12, 58%; median BMI 32.5 kg/m^2; range 24.4–44.3), excess proteinuria (median UPE of 4.2 g/24 hr; range 1–5–11.9), and kidney dysfunction (median eGFR 90.1 ± 45.5 mL/min/1.73 m^2; range 50.7–76.7). In 2 patients participating in the dosing extension phase and were followed for a median of 22 months. Patients received median 1 course of 12 weekly doses of narsoplimab per year (range 0.7–2.5 courses), with 58% (7/12) receiving ≤ 1 course per year. eGFR rate of decline was 5.2 (±1.2) mL/min/yr vs 8.6 (±3.7) mL/min/yr in the Leicester IgAN control cohort, suggesting better eGFR stability in the patient population. Over 3 years, eGFR improved in 25% (3/12) of patients. UPE decreased 38% from baseline through the follow-up period. Narsoplimab was well tolerated with no treatment-related serious adverse events reported.

**Conclusions:** In this Phase 2 study, narsoplimab was well tolerated. Treatment in patients with severe IgAN resulted in proteinuria reduction and better renal protection via eGFR stability relative to a matched comparator group.

**Funding:** Commercial Support - Omeros Corporation
PO2544
Early Changes in Estimated Glomerular Filtration Rate Post-Initiation of Empagliflozin in EMPEROR Heart Failure Trials
Faiez Zannad,1 João Pedro Ferreira,2 John Gregson,1 Sibylle J. Hauske,4 Bettina J. Kraus,1 Michaela Matthes,1 Javed Butler,1 Gerasimos Filipiatis,1 Christoph Wanner,1 Stefan D. Anker,1 Stuart Pocock,1 Milton Packert.2 EMPEROR-Preserved Trial Committees and Investigators 1Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; 2CHRU Nancy - Hopitaux de Braibois, Nancy, France; 3London School of Hygiene and Tropical, London, United Kingdom; 4Boehringer Ingelheim, Ingelheim, Germany; 5University Hospital, Wuerzburg, Germany; 6University of Mississippi School of Medicine, Jackson, MS; 7Atikou University Hospital, Athens, Greece; 8Charité Medical School, Berlin, Germany; 9Baylor Heart and Vascular Institute, Dallas, TX.

Background: Sodium glucose co-transporter 2 inhibitors (SGLT2i) may induce a early post-initiation eGFR decrease which does not impact the SGLT2i benefits in patients with diabetes. The occurrence, characteristics, determinants, and clinical significance of eGFR change among patients with heart failure are yet to be described. We report here the results in EMPEROR-Reduced, with reduced ejection fraction (HFREF). Results of EMPEROR-Preserved, in 5,988 patients with preserved ejection fraction (HFPEF), a trial a which just terminated, will be reported at the ASN meeting. The aim is to describe eGFR change from baseline to week 4 (as % of change relative to baseline) and assess its impact in EMPEROR-Reduced.

Methods: Landmark analyses (week 4) were performed assessing the risk of outcomes across tertiles of eGFR change.

Results: eGFR change was available in 3,547 patients out of 3730 (95%). Empagliflozin induced a leftward distributional shift of early eGFR changes with more patients with an initial eGFR decline. In the empagliflozin group, applying multiple adjustment methods, the risk of cardiovascular and renal outcomes was not increased in patients in whom early post treatment initiation eGFR decreased as compared to patients in whom it increased or did not change. However, in the placebo group, patients in whom early post treatment initiation eGFR decreased had a higher risk of sustained worsening kidney function compared to patients in whom eGFR increased.

Conclusions: In EMPEROR-Reduced, modest post treatment initiation eGFR decrease was observed more frequently with empagliflozin than with placebo. Only in patients taking placebo eGFR decrease was associated with a higher risk of sustained worsening kidney function. Any post-empagliflozin kidney function decrease in eGFR did not deprive patients from benefitting from empagliflozin therapy. Full results of these analyses in EMPEROR Reduced as well as results of similar analyses in EMPEROR-Preserved, with preserved ejection fraction (HFPEF) will be reported at the time of the meeting.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

PO2543
Serum Aldosterone and Urine Electrolytes Dynamics in Response to DASH Intervention: An Inpatient Mechanistic Study
Dana Bielopolski,1 Adam Qureshi,1 Andrea Romming,1 Jonathan N. Tobin,1,2 Rhonda Kost.1,3 The Rockefeller University, New York, NY; 2Clinical Directors Network Inc. New York, NY.

Background: The Dietary Approaches to Stop Hypertension (“DASH diet”) is a proven intervention to treat hypertension and is as effective as one antihypertensive drug. Despite years of research the precise understanding of its mechanism of action is lacking. We designed a translational trial to elucidate the biological pathway leading from nutritional change, through hormonal response, variations in urine electrolytes to blood pressure (BP) reduction.

Methods: A single center interventional trial. Stage 1 hypertensive otherwise healthy volunteers were admitted for 14-days, transitioning from American style diet to the DASH diet. Data were collected daily for vital signs, blood (chemistry) and urine (electrolytes). On days 1 and 10, participants completed 24-hour ambulatory blood pressure monitoring (ABPM) and 24-hour urine collections.

Results: 9 volunteers completed the protocol (7 men, 8 Black participants). Serum Aldosterone increased from day 0 (mean 8.3, range 2.8-18.9) to day 5 (mean 17.8, range 10.2-27.2) after intervention, and decreased on day 11 (mean 11.5, range 4.8-18.2) despite continuous exposure to the diet (p-value= 0.001). Urine ([Na]/[K]) electrolytes ratio (Picture 1) decreased from a mean of 3.5 before intervention on day 1 to 1.16 on day 4. BP reductions on 24-hour ABPM from day 1 to 10 were observed for the entire period, and during both sleep and awake recordings.

Conclusions: Shifting from a high-sodium/low-potassium diet to the opposite leads to serial physiological changes that are governed by Aldosterone and result in blood pressure reduction. Clinicians should follow urine electrolytes ratio to assess adherence to nutritional recommendations.

Funding: Other NIH Support - This work was supported by the Young Investigator Grant of the National Kidney Foundation. This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, to nutritional recommendations.

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Funding: Other NIH Support - This work was supported by the Young Investigator Grant of the National Kidney Foundation. This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, to nutritional recommendations.
PO2546

Effect of Empagliflozin on Kidney Biochemical and Imaging Outcomes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF)

Matthew M. Lee,1 Sarah Allwood-Spiers,2 Pauline Hall Barrientos,2 Kirsty Wetherall,3 Alex Mcconnachie,1 Paul Welsh,1 Giles Roditi,1 Steven Sourbron,3 Aleksandra Radajtovic,1 John McMurray,1 Pardeep Jhund,1 Mark C. Petrie,1 Naveed Sattar,1 Patrick B. Mark,1 SUGAR-DM-HF Investigators 1University of Glasgow, Glasgow, United Kingdom; 2NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; 3The University of Sheffield, Sheffield, United Kingdom.

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of worsening kidney function in patients with diabetes, and heart failure with reduced ejection fraction (HFREF). We explored the mechanisms underlying this benefit using magnetic resonance imaging (MRI).

Methods: We designed a multicenter randomized, double-blind, placebo-controlled trial to investigate the renal effects of empagliflozin in patients with left ventricular ejection fraction (LVEF) ≤40% and type 2 diabetes or prediabetes. Patients were randomized 1:1 to empagliflozin 10 mg once daily or placebo. Pre-specified exploratory outcomes included change from baseline to 36 weeks in kidney MRI biomarkers: kidney blood flow measured by a arterial spin labelling (pCASL) and b magnetic resonance renography (MRR), T1, apparent extracellular volume (aECV), volume.

Results: We randomized 105 patients: mean age 68.7 [SD 11.1] years, 77 (73%) male, 82 (78%) diabetes, mean eGFR 67 [22] mL/min/1.73m², mean urinary albumin:creatinine (uACR) 73 [27] mg/g. Compared with placebo, empagliflozin reduced right whole kidney (WK) and right cortex (Cx) pCASL by 27 (95% CI, -49 to -5; P=0.017) and 27 (95% CI, -51 to -4; P=0.024) mL/100mL/min respectively, reduced right WK aECV by 4.2 (-7.8 to -0.7; P=0.002) %, and reduced urinary sodium concentration by 15 (-26 to -4; P=0.009) mmol/L. Similar results were seen for left WK pCASL, left Cx pCASL and left WK aECV. There were no between-group differences in MRR, kidney T1, total kidney volume, eGFR, uACR or fractional sodium excretion.

Conclusions: Empagliflozin reduced kidney blood flow measured by pCASL, but not by MRR, in patients with HFREF and type 2 diabetes or prediabetes. Reduction in kidney blood flow may be a mechanism by which SGLT2 inhibitors reduce the risk of worsening kidney function in HFREF.

Funding: Commercial Support - Boehringer Ingelheim

PO2547

Vitamin K1 Retards Progression of Cardiovascular Calcifications in Hemodialysis Patients: The VitaVasK Trial

Turgay Saritas,1 Sebastian D. Reinartz,1 Thilo Krueger,2 Pieter Evenepoel,3 Michel Y. Jadoul,4 Christoph Kopp,5 Markus Ketteler,6 Peter Stenvinkel,1 Ralph Westenfeld,6 Stephanie Wied,6 Robert Steipman,7 Ralf-dieter Hilgers,7 Leon J. Schurgers,2 Jürgen Fleohe,7 University Hospital RWTH Aachen, Aachen, Germany; 2DeViTa, Geelenkirchen, Germany; 3University Hospital, Sts Leuven, Leuven, Belgium; 4Cliniques Saint-Luc, University of Louvain Medical School, Brussels, Belgium; 5Robert-Bosch-Krankenhaus GmbH, Stuttgart, Germany; 6Karolinska Universitetssjukhuset i Huddinge, Huddinge, Sweden; 7Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; 8University Maastricht, Maastricht, Netherlands; 9Universitätsklinikum Erlangen, Erlangen, Germany.

Background: Cardiovascular calcifications are prevented by matrix Gla protein (MGP), a protein activated by vitamin K. As HD patients exhibit marked vitamin K deficiency, the VitaVasK Trial (EudraCT No: 2010-021284-14) analysed whether vitamin K1 supplementation affects progression of coronary artery calcifications (CAC) and thoracic aortic calcifications (TAC) in these patients.

Methods: This prospective, open-label, multicenter trial randomized patients with preexisting CAC to continue on standard care or to additionally receive 5 mg vit K1 orally thrice weekly. Primary end points were progression of TAC and CAC volume scores in CT scans during 18 months. Repeated linear mixed effects models assessed the treatment effect after adjusting for study site.

Results: Of 60 randomized patients, 20 dropped out for reasons unrelated to vit K1, resulting in 23 control and 17 vit K1 patients. The trial was stopped early due to low recruitment rate. TAC progressed significantly between baseline and 18 months but its progression was reduced by a mean of 56% in the vit K1 compared to the control group at 18 months (p=0.039) (Table). CAC significantly progressed within the control group, but not within the vit K1 group. Progression at 18 months was lower by an average of 68% in the vit K1 group compared to the control group (p=0.072). Inactive dp-ucMGP in plasma was elevated at baseline, confirming vit K deficiency. Levels at 18 months were 110±40% of baseline in controls but rapidly dropped in the vit K1 group to 27±12% at 18 months. No treatment-related adverse events were noted.

Conclusions: Despite early termination, this randomized trial identifies a highly effective mode of correcting the vit K deficiency in chronic HD patients. Our intervention is potent, safe and cost-effective to reduce progression of cardiovascular calcification in this high-risk population.

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

Changes in volume score versus baseline within groups

<table>
<thead>
<tr>
<th>Vitamin K1</th>
<th>Baseline vs. 12 months</th>
<th>Baseline vs. 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymine aECV</td>
<td>0.06 (0.01, 0.11)</td>
<td>0.07 (0.02, 0.12)</td>
</tr>
<tr>
<td>Coronary aECV</td>
<td>0.08 (0.03, 0.13)</td>
<td>0.09 (0.04, 0.14)</td>
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</tbody>
</table>

Data are means (SE), adjusted for study site, and p-value. * p<0.05 versus vitamin K1

PO2548

Attenuated COVID-19 Severity in the MDR-101 MLK MERCURY Tolerance Study

Sam Kant,1 Sanjeev Akkina,2 William S. Asch,3 Daniel C. Brennan,4 Johns Hopkins University Hospital, Baltimore, MD; 5Loyola University Health System, Maywood, IL; 6Yale University School of Medicine, New Haven, CT, Medeor Therapeutics, San Francisco, CA.

Background: Transplant recipients are at high risk for COVID-19 infection and associated complications. This risk has correlated with use of immunosuppression. We describe an ongoing Phase 3 trial of a regimen to induce tolerance via mixed chimerism and functional tolerance with withdrawal of immunosuppression, and course of COVID-19 in patients participating in this study.

Methods: This is a prospective randomized multicenter open label-controlled trial to achieve sustained withdrawal from immunosuppression for 24 months without evidence of rejection, with enrollment of 30 patients with a 2:1 randomization of investigational and control patients. The investigational product MDR-101 (consisting of donor derived CD3+ hematopoietic stem and progenitor cells and a specified dose of CD3+ T cells) is administered post total lymphoid irradiation (TLI), 11 days post kidney transplantation with rabbit-anti-thymoglobulin induction and maintenance immunosuppression with prednisone for the first 10 days and mycophenolate mofetil on days 11-39 only. A calcineurin inhibitor (CNT) taper is initiated in those subjects who achieve a 6 month or greater period of persistent mixed hematopoietic chimerism (comprising at least 5% donor cells) coupled with the absence of de novo donor specific antibody (dnDSA), graft versus host disease (GVHD), transplant kidney loss, or biopsy proven acute rejection (BPAR) on a for cause or transplant kidney protocol biopsy.

Results: Two patients in the active arm developed COVID-19 (patient 1 at day 57 and patient 2 at 651 post enrollment; prior to introduction of vaccines). The COVID-19 infection in patient 1 presented with myalgias with minimal respiratory symptoms that did not warrant supplemental oxygen or mechanical ventilation. A prolonged course of myalgias persisted for 3 months despite resolution of the infection, with eventual tapering of CNI at day 186 post engraftment. Patient 2, completely off immunosuppression, presented only with mild URI symptoms that resolved without any sequelae.

Conclusions: Induction of tolerance with concomitant withdrawal of immunosuppression may aid not only in reduction in adverse effects of immunosuppressive drugs, but immune reconstitution to attenuate severity of COVID-19. Further larger studies are required to ascertain this effect in a larger population.

Funding: Commercial Support - Medeor therapeutics

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

B12